ENDOCRINOLOGY

THE BULLETIN OF THE ASSOCIATION FOR THE STUDY OF

INTERNAL SECRETIONS

Volume 19, Number 2 MARCH-APRIL, 1935 Serial No. 100

# PHYSICAL ASSOCIATIONS IN ADULTS WITH BEHAVIOR PROBLEMS*

ALLAN WINTER ROWE,† PH.D., AND MIRIAM VAN WATERS, PH.D.

*Evans Memorial, Massachusetts Memorial Hospitals*

BOSTON

Some years ago, one of us reported the results of an analytical survey of the various physical abnormalities presented by a group of children with behavior problems (1). At the time of presentation, it was recognized that the statistics were incompetent to indicate more than a possible trend of association since the children had been referred primarily for physical ailments and the behavior problem was in many instances only a secondary factor in the picture. With this group, however, evidence of injuries to the central nervous system and of disturbed pituitary function appeared with a frequency that challenged attention and warranted further study.

In a subsequent investigation on the association of endocrine disorders with psychoses and psychoneuroses (2), a high incidence of evidences interpreted as indicating incretory abnormality was observed. Further, there was apparently some degree of selectivity in the association between a given endocrinopathy and one or another type of mental aberration; illustrations are the high incidence of apparent pituitary dysfunction in cases with dementia praecox, and of ovarian failure with psychoneuroses of the hysteric type. Here, again, it should be emphasized, the data indicated no more than trends of association, suggestive, but in no sense definitive.

It has long been recognized that certain endocrine states are frequently associated either with changes in the individual personality pattern or with the development of characteristics which were latent during the years of normal glandular function. With the adult, at least in the non-mental group, there is a sense of social obligation and a certain social experience which does lead and may enable them to adapt the new personality to the old unchanged environment. With the child, on the other hand, both of these social agencies are lacking or but imperfectly developed, and thus the failure to reconcile the new personality with the old environmental conditions may readily engender a behavior problem of varying

*Read before the Eighteenth Annual Meeting of the Association for the Study of Internal Secretions, Cleveland, June 11, 1934.

†Deceased.

degrees of significance. Disturbed endocrine function, naturally, is not the only physical agency associated with such pattern changes; the effect of encephalitis on the child personality is but one well known example among the many. Further, it again must be stressed that the existence of the physical agent is not with any certainty associated with a changed mental and behavior status. In the children's series already cited (1), only one-sixth of the entire group presented behavior problems, although all of them had one or another of the physical backgrounds characterizing the behavior problem section.

As has already been noted, the trends disclosed by the earlier studies lacked a certainty of definition since all of the children were referred primarily for the resolution of existing physical ailments. A far clearer picture should result where studies were confined to a group in which the behavior problem was the sole common factor. On this basis, a programme of investigation has been formulated, and the present paper deals with the preliminary report on a survey of a consecutive series of one hundred adults, all inmates of a corrective institution, the Massachusetts State Reformatory for Women.*

Two patients at a time have been transferred from the institution to the Evans Memorial and have there remained in residence for not less than seven days. An elaborate routine of test and observation—the so-called "Long Form" (3) study—has been carried out uniformly on each patient, and, in addition, such other procedures have been included as were indicated for the individual case. The basic routine comprised, in addition to the medical history and a thorough physical examination, comprehensive blood and urine studies, the respiratory, protein, and carbohydrate metabolism, and some simple biometry. Also in the routine programme were included complete examinations of the eye, ear, nose, throat, chest, pelvis, and nervous system, by specialists in these several fields, and were supplemented by an audiogram and cardiogram as well as a duodenal function and rather complete radiological studies. At the completion of the study of each individual case, all of the data were collated and the diagnostic pattern defined. From the standpoint of primary etiology, the series may be divided into two nearly equal groups, namely, those patients who gave evidence of an endocrinopathy and those who gave none ("non endocrine"). The distribution of the endocrine diagnoses are presented in the first table.

TABLE I

DIAGNOSIS

ENDOCRINE GROUP

| Condition | Primary | Secondary | Total |
|---|---|---|---|
| Pituitary, dysfunction | 18 | 2 | 20 |
| Pituitary, failure | 9 | 0 | 9 |
| Gonad, failure, surgical | 1 | 1 | 2 |
| Gonad, failure, functional | 14 | 0 | 14 |
| Gonad, failure, gonorrhoea | 0 | 10 | 10 |
| Thyroid, failure | 11 | 3 | 14 |
| Pancreas, failure | 1 | 0 | 1 |
| | 54 | 16 | 70 |

Eighteen of these patients presented objective evidences consistent with primary pituitary dysfunction and nine more, making a total of

*This study has been carried out under the permission and with the sanction of the Commissioner of Correction of the Commonwealth. It is a particularly pleasant duty to express our appreciation severally to Commissioner A. Warren Stearns, Francis B. Sayre, and Frederick J. Dillon, all of whom have graciously co-operated in making this study possible.

twenty-seven, with pituitary failure. In addition, two more patients, with demonstrated lesions of the central nervous system, gave evidence of pituitary complications secondary to it. The ovarian failures are subdivided by causation into three groups. The patient in whom castration was a secondary factor was the single individual with diabetes recorded lower in the table. Some years previously, when operated upon for the removal of a cystic ovary, it was found that the other had been removed at an earlier operation. The case is one of a technical "pluriglandularity"; the diabetes presents as the primary present disability. In the functional group of ovarian failures, one-half gave evidences, which could be interpreted in terms of an earlier pituitary aberration which had spontaneously normalized during the intervening years, leaving behind certain suggestive somatic residua such as cranial dysplasia (v.i.), pelvic hypoplasia and the like. One of us (A. W. R.) has already mentioned such a sequence elsewhere in the literature; the supporting evidences at present are incompetent to define this as a syndrome; data have already accumulated, however, which warrant a tentative expression of the possibility of some such relationship. The known dominant influence of the pituitary on the ovary during the earlier developmental stadia is certainly not inconsistent with such an hypothesis. At present, however, a proper conservatism determines the classification of these cases among the functional gonad failures. Ten of the women with ovarian failure had past or present gonorrhoea. While it is by no means certain that all of the evidences of endocrine failure presented by this group were of infective origin, it is more appropriate to recognize this possibility and list as primary only those glandular cases from which possibly causal complications are absent.

The eleven cases designated as primary thyroid failures are supplemented by three more in which the glandular failure is apparently secondary and sequential to a long-continued toxaemia in which the liver and gall-bladder play the primary roles. This association has previously been described (4). Comment has already been passed on the single diabetic in the series.

Turning to the remaining cases in the series, in which no evidence of glandular involvement was detected, the etiological classifications are given in Table II.

TABLE II

DIAGNOSIS

NON-ENDOCRINE GROUP

| Condition | Primary | Secondary | Total |
|---|---|---|---|
| Lesions of the central nervous system | 8 | 9 | 17 |
| Hepatic dysfunction | 10 | 28 | 38 |
| Syphilis | 8 | 27 | 35 |
| Gonorrhoea | 13 | 35 | 48 |
| Tuberculosis | 2 | 16 | 18 |
| Psychosis and psychoneurosis | 1 | 19 | 20 |
| Pregnant, normal | 2 | 0 | 2 |
| Unclassified | 2 | 0 | 2 |
| | 46 | 134 | 180 |

In the first group, birth injury, fractured skull, one case with a cord lesion, and several post-encephalitic cases constitute the primary division; in the secondary series, the same factors are operative but with evidence of less serious and extensive damage.

Various types of hepatic dysfunction are diagnosed in over one-third of the group and are classified as primary in 10 per cent. The large number of chronic alcoholics in the series undoubtedly plays a part in producing so high an incidence of functional liver derangement. One-third of the group had had syphilis, and one-half gonorrhoea; twenty-four had had both; thus the venereal complication in the series is 59 per cent or nearly two-thirds. Two cases of lues were certainly of congenital origin and several more may have been. In view of the social background of the group and the large part played in it by so-called sex offenses, if there be anything remarkable in these figures it is that the percentage is not larger.

Two women showed active pulmonary tuberculosis, while sixteen more had evidence of past or present infection as a secondary feature in their diagnostic pictures. One woman was frankly psychotic and nineteen more gave evidence of a secondary mental disorder. Two of the younger patients were examined during apparently normal pregnancies, and with the remaining two cases one crucial observation is lacking in each and they are thus reported as unclassified. Both, however, gave no evidence of glandular involvement and so fall appropriately in the non-endocrine group. Summarized briefly, 4 per cent gave evidence interpreted in terms of a primary endocrinopathy and 16 per cent more presented a secondary and sequential incretory factor. Convincing evidences of lesions of the central nervous system play a less significant role than in the children's series already cited (see Table V) but are none the less recorded with an appreciable frequency.

It is perhaps worthy of comment that this group of one hundred women, all of whom were ambulatory and, with but rare exception, employed in some activity in the institution, presented nearly two hundred and fifty significant departures from normal health. Further, to these should be added the even more numerous reports of abnormal conditions which have not been listed among the primary manifestation. To report but a single group, radiography afforded evidence of six cases of cholecystitis, of three with gastric ulcer, and of ten patients with active appendicitis.

Before discussing the pertinent details of the physical study, the data from which the foregoing diagnoses derive in part and from the analysis of which, it is hoped, that further information may be adduced toward the solution of the present problem, a brief review of the behavior classification of the series may be considered.

TABLE III

BEHAVIOR CLASSIFICATION

| Class | Sherborn | State Prison |
|---|---|---|
| Theft | 30% | 51% |
| Sex | 54% | 22% |
| Homicide | 3% | 25% |
| Alcoholism | 9% | .... |
| Miscellaneous | 4% | 2% |

The great majority of the offenses involved can be conveniently grouped under one of the three major captions of (a) theft, (b) sex, and (c) homicide. For purposes of rough comparison, figures drawn from a survey of the male population of the State Prison in 1929 are added (5). It should be noted at once that these are not comparable groups. The men have all committed felonies, commitment being with a minimum sentence of two and one-half years; on the other hand, many of the women are sent to the Reformatory for misdemeanors with a minimum term of but one year. In the sex offenses, which constitute one-half of the women's series, rape for obvious reasons does not appear, and incest is but of relatively rare occurrence. These are the principal offenses in the sex fraction of the male group. Our female homicides were all abortionists; the homicide fraction in our present study group is not strictly representative of

the Reformatory population. Roughly, in the present series, a sex offense in some form characterizes one-half, and theft one-third of the entire group. Many of the women were habitual offenders with long and varied records of offense. A more complete analysis of this phase of the study is reserved for a later communication.

Turning now to the survey of the physical and physiological elements in the group, which is the basis of the present report, the age data first come to attention.

TABLE IV
AGE

| Datum | Amount |
|---|---|
| Oldest ..... 63 years | |
| Youngest ..... 15 years | |
| Less than 21 years ..... | 26 |
| 21 to 30 years ..... | 38 |
| 31 to 40 years ..... | 19 |
| 41 to 50 years ..... | 12 |
| Over 50 years ..... | 5 |
| Average ..... 28.8 years | |

Nearly two-thirds are less than thirty years of age and only five are over fifty. The average age of twenty-nine years calls for interpretation in terms of the recidivism which was noted in the preceding section. An early onset of the behavior problem is the rule, rather than the exception, in the series as a whole. Thus demonstrated physical factors of long standing as, for example, those indicative of pituitary malfunctions that have engendered well defined and classifiable cranial dysplasias, are brought more closely into association—not, be it noted, necessarily a causal-resultant relationship—with the development of the behavior problem.

In the children series, head trauma figured in a very important proportion of the series. Using the data from this group as a control, comparison is made with the equivalent reports from our current study series.

TABLE V
HEAD TRAUMA

| Cause | Number | Control* |
|---|---|---|
| Birth ..... | 5 | 21 |
| Later mechanical injury ..... | 15 | 22 |
| Encephalitis ..... | 4 | 9 |
| Total ..... | 24 | 52* |
| General trauma with possible head involvement ..... | 15 | |
| | 39 | |

*In addition, 7 gave physical evidence of neural involvement.

Patently, the record of neural lesions, actual or potential, is appreciably less in the Sherborn group. Of the twenty-four examples here listed, only seventeen find record in the earlier table (II); the remainder of the subjects gave no current evidence of any organic involvement during the neurological examination. Strictly, the two congenital syphilitics should be added to our present group; even with their inclusion, the tale would fall far short of the children's report. Once again let it be emphasized, however, that the latter were all known to be in ill health while the Sherborn group was a cross section of a presumptively reasonably healthy population. A neural factor may reasonably be adduced for at least a fifth of the adult series, and in certainly 10 per cent as a minimum, injury occurred in the very early stadia of life.

Developmental defects or abnormalities may properly be regarded as evidences of past or present functional derangements, and the more significant of these have been collected in Table VI.

TABLE VI
DEVELOPMENTAL ABNORMALITIES

| Datum | Incidence |
|---|---|
| Microcephaly | 1 |
| Rachitis | 4 |
| Cleft Palate | 2 |
| Bicornate Uterus | 1 |
| Dwarf (135 cm.) | 1 |
| Sitting Height Index, low | 16 |
| Sitting Height Index, high | 20 |
| Overweight (average +39%) | 32 |
| Underweight (average −17%) | 17 |

In largest measure, the data speak for themselves. The patient with the bicornate uterus (B-2040) was a prostitute, twenty-five years old, with earlier lues and gonorrhoea. A laparotomy for an appendectomy showed a small bicornate uterus and two very small atrophic ovaries. The subject had never menstruated. The external genitalia were hypoplastic. Functional ovarian failure was the primary diagnosis; a pituitary background was probable. In addition to the one dwarf, there were six other women less than five feet tall. The average sitting height index of the adult female in this country is 0.533; the normal range may be designated as from 0.520 to 0.545 with a borderline zone on either side extending those latter limits appreciably. In the present group, sixteen gave positively low indices (relative overgrowth of the long bones) with an average of 0.513, while twenty showed the opposite condition (in some instances, at least, due to early epiphyseal closure) with an average of 0.554. The body weight relations are less certainly evidences of functional derangement, as in the case of obesity, at least, the indulgence of a healthy appetite is the most frequent cause. In the present instance, however, we are dealing with an institutionalized population whose supervised diet is liberal but not excessive. During the period of hospitalization, where like conditions prevailed, the nitrogen output was well above a maintenance level (average of 8.80 grams) but indicated no excess. Only two in the group showed really high nitrogen values; in one of these the weight was 80 per cent above prediction, the other only +19 per cent. With the relatively high incidence of gastrointestinal disorders of various sorts, it is not suprising that an appreciable number (22 per cent) showed nitrogen outputs below 7 grams. This exceeds the number who were significantly underweight. The general impression from this group of evidences is one of a frequency of developmental and metabolic errors in excess of the usual community incidence. Again, many of these must date from early in the life of the individual.

The catamenial history may give further information on the relative normality of a function so profoundly influenced in its initiation and conduct by various developmental agencies. For purposes of control, data previously reported elsewhere (6) from a series of five hundred and twenty-five demonstrably normal women have been included.

TABLE VII
CATAMENIA (A)

| Age of Onset | Sherborn | Control |
|---|---|---|
| Less than 12 years* | 14% | 5.5% |
| 12 to 14 years† | 70% | 75.1% |
| Over 14 years | 16% | 18.4% |

*One each at 8 and 9 years.
†Two at 17, one at 18 years. One (25 years) never matured.

Early maturation was reported in one-seventh of the series, or more than twice as frequently as in the control group. Late onset, on the other hand, is slightly more frequent in the normal series; exception may be taken to the limits assigned by implication to the normal range. Data from a variety of sources indicates that in such a population as that under discussion, the great majority of normal healthy girls mature between the twelfth and the fifteenth birthday. In our present data, the early maturity seems to be the point of importance both as it indicates the early onset of change in those factors governing the mechanism of maturation and equally the social element of an incipient adult sexuality during the years of childhood.

The menstrual habit, once established, reflects the level of various functions, each of which may influence the rhythm and character of the period. Data from same control group (6) are used for comparison.

TABLE VIII
CATAMENIA (B)

| Rhythm | Number | Control |
|---|---|---|
| Regular— | | |
| 21 to 27 days | 5 | 8% |
| 28 days | 50 | 65% |
| 29 to 32 days | 19–74* | 15%–88% |
| Irregular— | | |
| Diminished | 2 | 2% |
| Both | 4 | 3% |
| Increased | 19–25* | 7%–13% |
| Type of Period— | | |
| Scanty | 8 | 9 |
| Normal average | 37 | 77 |
| Profuse + | 29 | |
| Profuse ++ | 25 | 14 |

*One case not matured.

The data are in largest measure self-explanatory. The control group shows an appreciably greater regularity, particularly in the modal rhythm of twenty-eight days. Those in the study group having irregularity show principally a lengthened intermenstrual period, a fact wholly consonant with the usual endocrine influences so liberally represented in the series. A striking feature of the periods themselves is that profusion seems to be the habit in the institution group, over half the subjects showing excess with half again of these exhibiting this feature in a marked degree. How far the venereal factor may play a part can be roughly estimated by further analysis. Allowing for the one subject with both lues and gonorrhoea who had never menstruated, the menstrual habit of the three groups can be presented in tabular form.

In so far as figures from so small a series may be meaningful, gonorrhoea would seem to conduce to a profuse period while syphilis shows an opposite association. A larger series could readily modify this conclusion. Further, deducting the twenty-nine venereal subjects with profuse periods from the total as reported, there yet remain twenty-five, giving double the incidence of profuse periods in the control group who exhibit the same abnormality. Analysis of the catamenial data warrants the conclusion that this function exhibits a definitely larger degree of abnormality than that shown by a normal series.

TABLE VIII-a
VENERAL DISEASE AND MENSTRUAL PERIOD

| Infection | Period | | |
|---|---|---|---|
| | Diminished (%) | Normal (%) | Increased (%) |
| Gonorrhoea | 8 | 22 | 70 |
| Syphilis | 20 | 40 | 40 |
| Both | 13 | 39 | 48 |

Fertility is another bodily function susceptible to subversive influences alike through glandular and non-glandular agencies. As the developmental is but the secondary and the functional the primary factor in this relationship, a control series of over twelve hundred cases previously reported (7) has been selected for comparison in which the composing members were allocated to the several endocrinopathies and a variety of non-glandular conditions in roughly the same proportions as in the study series. In the latter group, four of the women had not certainly been exposed—one was unquestionably a virgin—and the analysis deals with the remaining ninety-six.

TABLE IX
FERTILITY

| Datum | Number | Per Cent | Control |
|---|---|---|---|
| Exposed* | 96 | .. | ..... |
| Never pregnant | 27 | 28 | 24.0% |
| Conceptions (69 women) | 221 | .. | ..... |
| Children | 150 | 68 | 74.3% |
| Miscarriages | 47 | 21 | 20.0% |
| Abortions (9 women)‡ | 22 | 10 | 5.7% |
| Pregnant | 2 | 1 | ..... |

*Positive evidence.
‡One woman each with 8, 5, and 3 abortions, respectively, and 6 more with 1 each.

The Sherborn group shows a slightly higher but scarcely significant degree of infertility than does the control. On the other hand, the institution series shows a higher initial fecundity (an average of 3.2 conceptions as against 2.8 in the control series). The other data show a very definite parity as regards potential fertility, the major discrepancy resting upon the larger number of induced abortions reported by the institution group. It is of passing interest, perhaps, that gonorrhoea seemingly plays so small a part in influencing fertility. Where mechanical obstruction is a result, sterility naturally ensues; without the production of an actual physical impedence, Neisserian infections are apparently of but minor import. One of us has had occasion to note the same conditions in the male in the course of studies on the problem of human infertility. In short, the institution group shows a fertility practically equivalent to that of a much larger control series, the members of which present the same functional and organic disabilities which characterize the former.

Medical histories are, at best, the most subjective of the evidences available for analysis in terms of the patients' reports. Particularly is

this true with such a group as that under investigation; further, the earlier social circumstances of not a few in the series conditioned a real ignorance of their earlier years. As an illustration, thirty of the group were unable to give any family history, and many of the others as given were fragmentary and expressed negations not to be regarded as wholly reliable. Verification from outside sources and records was sedulously sought, but, naturally, with but partial success. Thus figures as secured are no more than minima and in isolated instances may derive some added weight from this fact. In the main, however, but minor report will be made of this group of evidences as the items lack a factual authority in so many of the records. Further, for purposes of the present investigation, evidences of growth or developmental aberration or long-standing functional derangement or organic lesion are more pertinent to establish associations with the onset of the behavior problem which is the sole factor presented in common by all of the group.

Operative histories were in large measure susceptible of verification. Thirty-six subjects had had one or more laparotomies, comprising appendectomies (24), salpingectomies (12), ovariectomies, one or both (7), hysterectomies or suspensions (6), Caesarian deliveries (5), together with several herniotomies and three gall-bladder operations. The high incidence of association of functional ovarian failure with abdominal section renders this datum of possible significance from the standpoint of chronology.

For the reason given above, but few of the details of the physical examinations need be recorded. Certain of them are intrinsic in the diagnostic pictures already summarized, certain others will be touched on later. Analysis of the blood and urine findings, while they are of basic importance in establishing certain aspects of the individual diagnostic picture, are but ill adapted to presentation in limited compass. The urine analyses gave evidence of a rather frequent incidence of renal irritation, but the chemical examination of the blood indicated but two individuals to exhibit a real lowering of renal permeability. Secondary anaemia was a common finding, and the leucocyte patterns reflected the characteristic pictures of the conditions with which they are associated.

A few of the factual evidences may be touched upon more in detail as they present a somewhat greater specificity in their indications than do the equally important but less individually characterized results of the other laboratory approaches. Among this former group is the respiratory metabolism.

TABLE X

RESPIRATORY METABOLISM

| | Number | Average Deviation or Reading |
|---|---|---|
| Basal Rate— | | |
| Unsatisfactory, (markedly) | 13 | −4% |
| Satisfactory, normal | 17 | −4% |
| Unsatisfactory | 15 | −17% |
| Satisfactory, abnormal | 55 | −18% |
| Blood Pressure, Systolic— | | |
| Above 140 mm | 3 | 147 mm. |
| Normal | 20 | 116 mm. |
| Below 110 mm | 77 | 98 mm. |
| Pulse Rate— | | |
| Above 90 | 1 | 100 |
| Normal | 17 | 76 |
| Below 70 | 82 | 60 |

Complete authority for this measurement is difficult of attainment as all of the unavoidable errors operate in one direction and yield observed values in excess of the truth. Repetitions of the test for purposes of education are frequently helpful, but arithmetical results must always be regarded with critical suspicion and a real flexibility exercised in their interpretation. Many tests are recognized as unsatisfactory and unreliable at the time of performance; others may be apprehended only when frequent repetition of the test ultimately leads toward a true basality on the part of the subject.

In the present series, in which nervous instability was a common condition, never less than two entirely independent series of records were made and, when possible, this number was increased as far as was reasonable. In spite of these precautions, thirteen of the group yielded results falling in the conventional normal zone and known to be too high, while fifteen more but slightly less unsatisfactory and non-representative reports were yet in the definite range of hypofunction. An inspection of the data in the table will show that the whole tendency is toward a lowered metabolic level. The endocrine cases—all hypofunctional—will account for the largest number of established cases, while malnutritional agencies are undoubtedly responsible for the majority of the remainder, none of whom exhibit an incretory deficiency. From whatever causes—and they are several—the group as a whole is characterized by a lowered oxygen exchange. The blood pressures and pulse rates reflect the same general tendency. Body temperatures (oral), on the other hand, either are or approximate the normal in those cases in which some recognized depressive agency like thyroid failure is not operative. The picture is one of a lowered energy exchange and one, presumptively at least, of some degree of chronicity.

In like manner, the galactose tolerance reflects the influence of a number of regulatory agencies. Further, when two opposing influences operate simultaneously in the same individual the end result is the algebraic sum of both, each expressed in terms of its influence. To illustrate, thyroid failure tends to raise, hepatic dysfunction usually to lower the utilization capacity for this sugar. A nice balancing of these antagonistic agencies in the same individual may yield a depressed, normal, or increased tolerance as one or the other predominates in influence.

TABLE XI

GALACTOSE TOLERENCE

| Deviation | Number |
|---|---|
| Above +50% | 1 |
| +50% | 6 |
| Normal | 10 |
| −25% to −50% | 53 |
| Below −50% | 24 |
| Incomplete | 6 |

Seven show an increased tolerance, and seventy-seven various degrees of depression. Only ten of the completed tests yield normal values, and

three of these are at the prepuberal level of 20 grams, being severally a castrate, the non-matured case, and a normal pregnancy. Here, again, although the causal agents are highly diverse, one finds clear-cut evidence of a predominant disturbance of the carbohydrate metabolism, so far at least as the sugar, galactose, is concerned. Barring the one established diabetic, the blood sugar levels are normal and only five of the total series show a glycosuria. Undoubtedly, repeated tests would demonstrate a much larger number of cases with intermittent glycosuria; such a condition has already been recorded (8) in normal pregnancy and other conditions engendering a disturbed carbohydrate metabolism.

A year ago, Mortimer (9) described four types of cranial dysplasia associated with various forms of disturbed pituitary function. Briefly, they may be characterized as follows:

Type I. Diploic expansion with marked hyperpneumatization; the characteristic skull of uncomplicated acromegaly.

Type II. The same with later and secondary sclerosis, particularly of the middle and inner tables.

Type III. The antithesis of Type I with thin compact skull and hypopneumatization and arrest of sinus development, most strikingly shown in the frontal sinuses. The skull of Simmonds' disease and of congenital or early apituitarism.

Type IV. The same as III but with secondary changes involving sclerosis of the vault most marked in the frontal bone and with a persistence of the sinus arrest and general hypopneumatization characterizing the type (III) from which it derives.

Types I and III may be regarded as the pure types produced by a single level of pituitary malfunction. Types II and IV, on the other hand, demonstrate transitional features produced by later changes in the level of glandular activity. The presence of one of these cranial dysplasias is not certain evidence of current pituitary dysfunction but may warrantably be interpreted as evidencing a period of pituitary aberration of which the skull changes are permanent residua.

TABLE XII

CRANIAL RADIOGRAMS

| Datum | Incidence |
|---|---|
| Type I | 12 |
| Type II | 14 |
| Type III | 2 |
| Type IV | 14 |
| Total | 42 |

Forty-two of the patients in this series exhibit one or another of the characteristic pituitary patterns. The transitional forms II and IV account for more than half. With recognition of the limitation of current activity noted above, the agreement of this index with the diagnoses of pituitary involvement is most satisfactory. While a diagnosis of current pituitary dysfunction cannot be made from the unsupported radiographic evidence alone, the inference of a possible permanent or transitory hypophyseal element in the life history of the patient is definitely warrantable. Mortimer's later work (10), reported this year, presents a wealth of experimental data and is completely confirmatory.

A few of the special examinations merit brief report. Nineteen electrocardiograms gave evidence of heart abnormalities, and fifty audiograms showed significant impairment of hearing, many of the curves assuming the forms characteristic of lues or hepatic dysfunction as first recorded by Drury (11). Twenty-seven chest examinations disclosed cardiac or pulmonary disorder or both, and 35 per cent of the series gave positive evidences of organic neural damage of varying degrees of severity. Twenty-one instances of abdominal disorder were indicated, and there were but fifteen normal pelves in the entire series, although the abnormalities in twenty-seven were no more than the residua of child bearing. With forty-two of the group reporting previous tonsillectomy, thirty-five more disclosed infected tonsils. This latter figure is high, even in a series which includes so many endocrine and liver cases, conditions always showing a high incidence of association. Five of the women were edentulous, forty more had very poor teeth, while radiographic study disclosed five more with periapical infections. The dental status was far from good in the majority of the remaining 50 per cent.

With the wealth of information derivable from a complete ophthalmologic study, certain of the positive findings may receive mention.

TABLE XIII

EYE REPORT

| Datum | Incidence |
|---|---|
| Abnormal Pupils | 36 |
| Field Changes | 17 |
| Enlarged Blind Spots | 40 |

With the neural damage of both traumatic and specific origin, pupillary abnormality, as might be anticipated, was found in one-third of the entire series. Significant field changes were shown in one case with atrophy, and several each with neural damage, hepatic dysfunction, pulmonary disease, and in a few of the psychoneurotics. Blind spot enlargement, uni-lateral or bi-lateral, was exhibited by two-fifths of the entire series. Vascular sclerosis was a common report in the older members of the group.

In the foregoing discussion, but minor note has been made of possible mental factors. It is purposed to discuss this phase of the problem in a later communication. The actual mental acuity level of the group, however, may suitably be included here, as causal physical factors can be recognized in a proportion, at least, of the individuals exhibiting deficient or retarded mental development.

TABLE XIV

| Grade | I. Q. | Number | |
|---|---|---|---|
| Feeble minded | below 0.70 | 16 | |
| Boderline | 0.71—0.80 | 13 | 44 |
| Low Average | 0.81—0.90 | 15 | |
| Adult Average | 0.91—1.10 | 40 | |
| Superior Adult | 1.11 and over | 16 | 56 |

The data speak for themselves, but it is certainly informative that 44 per cent of this series fall in categories below that of the average adult, and one-sixth were frankly feeble-minded. In six of this latter group the diagnosis was primary pituitary disorder and in two more, ovarian failures with a possible pituitary background. Two more had neural damage as the primary condition; two showed evidence of thyroid failure. One of the pregnant girls, two of those with ovarian failure of Neisserian origin, and one patient with lues complete the series. In the last four, at least, the mental status may well be regarded as an agent possibly related to the reported primary condition; in the remainder of the group the converse may be assumed with some measure of reasonability.

DISCUSSION

In the body of the paper, but scant reference is made to existing literature, the few citations being purely expository of the text. There is a fairly extensive and somewhat uncritical literature dealing with physiological factors of assumed causation, and an even more profuse and frankly less critical array of texts dealing with the psychogenesis of crime. To the student in this debatable field the numerous details of existing controversies and the arguments pro and con are completely familiar. No good purpose can be served again to review a literature that has already been exhaustively studied. Further, the present authors wish to state that they have no thesis to prove, and no sweeping conclusions to draw, which require a supporting documentation of judiciously selected quotation.

The problem of human behavior as it relates to crime and misdemeanor is a vast one, calling for its ultimate resolution on the conjoint efforts of a great number of serious and critically-minded investigators following the many broad avenues of investigative approach which lead to the common goal. The purpose in the present report and in those which are contemplated to succeed it is to gather together factual data deriving from individuals who by common consent are felt to exemplify certain of the departures from conventional normal behavior. The whole basic question of motivation must for the present be left completely in abeyance; others equally vital to the successful solution of the problem must be likewise ignored. To be so overwhelmed by the magnitude of the problems involved as to predicate immediate defeat determines a mental attitude devoid of any element of construction. Equally, a reasonable humility concedes without argument the intrinsic limitations of studies like the present.

So to express with a due conservatism the indications of this present study, the following may be stated:

In a group of one hundred women, all committed to a corrective institution for classifiable offenses against public polity, clinical and laboratory studies have disclosed a very large amount of physical ill health both in the form of functional derangement and of organic disease.

In more than one-half of the series, evidences of functional disorders of the several ductless glands have been elicited; further, such endocrine dysfunctions are generally recognized as agencies associated with the establishment or modification of so-called personality patterns. Equally, in the non-endocrine moiety of the series are other individuals presenting functional or organic disorders which equally are conceded to influence the personality of the individual sufferer.

With personality patterns falling sufficiently outside of the tolerant range of the so-called normal zone, conflicts may and do arise with those rules of conduct deriving from the consensus of general normal opinion.

If the maladjusted personality derive from or be influenced by physical factors operative in the individual, then a correction of these agencies, when they be correctible, may, in turn, allow a return of the individual to

that personality more nearly in accord with the environmental influences to which it is subject. This statement is wholly and properly subjunctive; it offers no more than a working programme for further experiment and study.

Equally must it be borne in mind that the existence of these potentially subversive physical agencies in any individual does not inevitably produce a personality change referable to a common causal denominator. The endocrine and other conditions represented in our study series are found widely distributed throughout the community at large, existing in a great number of persons, none of whom present the behavior problems that characterize the tiny institutional group which has been investigated.

If there be a causal-resultant relationship—and this is very far from being established by our present knowledge—then in addition to the activating agent there must be a soil fertile to its action. Further, there is a relativity in the action of two or more such composing forces which permits literally an infinity of resultants to be derived from them. Tritely stated, differences may be of degree and of direction rather than of kind, and the aberrancy of the behavior estimated solely by its relative remoteness from the average.

Enough has been said to define a position, one not founded on preconception or dogmatism, and one maintaining, so we hope, a complete flexibility of adjustment to every fact that time may add to our meager store. As an encouragement to further endeavor by suggesting a trend of association, we would summarize this and two of the previously cited studies in tabular form.

TABLE XV

SUMMARY OF ENDOCRINE ASSOCIATION

| Series | Number | Endocrine % |
|---|---|---|
| Children | 104 | 65 |
| Psychoses | 110 | 76 |
| Psychoneuroses | 140 | 76 |
| Criminal | 100 | 54 |

The factor of association of apparent incretory abnormality appears with a frequency warranting further study to confirm or to deny its implication.

## SUMMARY

A consecutive series of one hundred inmates of the Massachusetts Reformatory for Women have been hospitalized for periods of seven days or more, and during this interval an elaborate programme of clinical and laboratory examinations have been carried out with each subject. On the basis of these studies, fifty-four of the group have been diagnosed as presenting one or another endocrine disorder as the primary condition, while the remainder of the series gave no indications suggestive of an incretory involvement, but did exhibit, with but minor exception, non-endocrine organic disturbances of significant gravity.

Special emphasis has been laid on the survey of evidences indicating growth and developmental abnormalities as evidencing functional aberrancy in the earlier stadia of life. This has been supplemented by a review of some of the current indications of significant metabolic disorder. Among the former, abnormal sitting height indices and cranial dysplasias are noted, together with individual patients with microcephaly, bicornate uterus, cleft palate, and the like. In the latter, abnormalities of menstrual habit, of respiratory and carbohydrate metabolism are reported. A depression of mental acuity below the average normal was shown by nearly half of the group; while this observation reflects the present status, the condition in many of these individuals is certainly one of long standing. Indications of neural damage were remarked in nearly one-fifth of the total series.

In short, in an ambulatory series of one hundred women, exhibiting as the only condition common to them all the presence of behavior problems which have brought them within the jurisdiction of the criminal laws, a very large amount of physical and physiological abnormality distributed throughout the entire group is indicated by diagnostic studies. The concurrence of diagnostic patterns consistent with certain incretory disorders and with other non-endocrine states, and those of the abnormal personalities which may have engendered behavior problems, indicates a trend of association which is potentially suggestive. Finally, the authors wish to reaffirm in no uncertain terms their complete unwillingness to read into these associations, interesting as they find them to be, any present implied causal-resultant relationship.

In conclusion, we wish to extend our appreciative thanks to the subjects of these studies whose cooperative willingness has so greatly facilitated the work. We express with much pleasure our indebtedness to Miss A. Gertrude Daley, from whom the psychometric data have derived, and especially to Dr. Helen M. Wiestling, for general supervision of the patients and of the corrective measures undertaken in their behalf subsequent to the completion of the diagnotic studies.

## REFERENCES

1. Rowe: Am. J. Orthopsychiat. **1**: 451. 1931. Endokrinologie. **9**: 179. 1931.
2. Rowe and Pollock: Endocrinology, **17**: 658. 1931.
3. Rowe: "The Differential Diagnosis of Endocrine Disorders." Williams & Wilkins, Balt. 1932.
4. Rowe: Endocrinology, **17**: 1. 1933.
5. "A Statistical Analysis of the Inmate Population of the Massachusetts State Prison," Sept. 1929. Issued by the Department of Correction.
6. Rowe: Endocrinology, **14**: 243. 1930.
7. Rowe: J. A. M. A. **95**: 1219. 1930.
8. Rowe, Gallivan and Matthews: Am. J. Physiol. **96**: 94. 1931.
9. Mortimer: Paper presented at the 17th annual meeting of The Association for the Study of Internal Secretions, Milwaukee, June, 1933.
10. Mortimer: Paper presented at the 18th annual meeting of The Association for the Study of Internal Secretions, Cleveland, June, 1934.
11. Drury: Ann. Oto. Rhin. & Laryng. **38**: 625. 1929. Ann. Oto. Rhin. & Laryng. **40**: 415. 1931.

# EXPERIMENT TO PRODUCE LACTATION IN CASTRATE WOMEN

AUGUST A. WERNER, M.D.
ST. LOUIS

Hildebrandt (1) and Halban (2) were the first to propound the theory that the placenta elaborates a substance that stimulates growth of the mammae and at the same time inhibits lactation. This idea which initiated the modern investigation of the problem of lactation resulted from the clinical observation that expulsion of the placenta was followed by secretion of milk, and retention of the placenta, by failure to lactate. Frankl (3) observed that implantation of placental tissue into rats near term prevented lactation following parturition, as long as the grafts remained active.

Stricker and Grueter (4), experimenting with rabbits, concluded that the action of the corpus luteum upon the mammary glands was necessary, before their anterior pituitary extract could produce lactation. (Their extract of the corpus luteum may have contained estrogenic substance.) Corner (5) reported that the administration of corpus luteum extract (progestin) to non-pregnant spayed rabbits did not cause proliferation of the mammary gland beyond the stage normally attained at puberty, and that the continuous presence of corpora lutea in the ovaries, during a period equal to that of normal gestation (brought about by experimental means) was equally ineffective in altering the mammary gland. Turner and Frank (6) reported a series of experiments in which gonadectomized immature rabbits were used. They found that daily injections of 20 rat units estrogenic hormone (theelin) for about 30 days caused growth of the duct system and slight lobule proliferation comparable to that of the mature virgin rabbit after continuous estrum. The injection of a physiologically active extract of the corpus luteum into gonadectomized rabbits, either with or without a previously developed duct system, was ineffective in stimulating the growth of the ducts or lobules of the mammary gland. Upon the simultaneous injection of theelin and corporin for 15 days, a hyperplasia of the gland lobules was observed resembling in every respect the growth of the mammary gland during the first 15 days of pregnancy or pseudo-pregnancy. They also found that glands so developed are capable of responding to the lactation-promoting hormone of the pituitary.

Edgar Allen (7) determined the effect of the estrus-producing hormone of ovarian and placental origin on the growth of the mammary gland of the monkey. The result showed marked growth and branching of the ducts with some increase in the number of the alveoli, and development of the nipple.

Werner and Collier (8) found in two experiments in which 13 castrate girls were treated with theelin, that marked activity of the breasts occurred, characterized by a sensation of fullness and actual enlargement, with development of the duct system (determined by palpation), erection of the nipples, and tingling and tenderness in the gland trees. At the present time it is rather generally believed that growth of the mammary glands depends upon stimulation by the ovarian estrogenic hormone which produces the pubertal condition and that both estrin and the luteal hormone are necessary to prepare the glands for the action of the lactation-inducing hormone of the anterior pituitary.

Nelson (9), after a rather exhaustive series of experiments in which guinea-pigs were used, concluded that, "the ovarian hormones are active in the production of mammary gland growth during pregnancy, but that they inhibit lactation during that period. The high content of ovarian hormone in the pregnant animal appears to inhibit the secretion of the lactation-inducing hormone of the anterior hypophysis, as well as to act directly upon the mammary glands. With the decline in ovarian hormone content at parturition, the inhibitory influences are removed, the lactation-inducing hormone is secreted, and lactation occurs."

"PROLACTIN"

Riddle, Bates and Dykshorn (10) have isolated a hormone from the anterior pituitary of beef, sheep and hogs, which induces a specific enlargement and functioning (crop-milk formation) of the crop gland in doves and pigeons. They have named this hormone "Prolactin." A number of research workers have successfully induced lactation under various experimental conditions, in rats, rabbits, guinea-pigs, dogs, cows, monkeys, etc., by the injection of hypophyseal extracts. It will be interesting and of much clinical value to determine whether prolactin will be effective in producing lactation in the human.

Kurzrok, Bates, Riddle and Miller (11) reported treatment of 37 women (with prolactin) delivered of normal children. Of these, 29 cases were chosen in which lactation had failed to develop adequately by the sixth day (fifth in two cases) or later postpartum. In 21 of these women there was a gain greater than 100 gm. of breast milk daily when comparison is made between the day preceding prolactin dosage and the date of the patients' discharge, three to nine days later. In four cases the gain was from 50 to 100 gm. According to their table, there was a loss in three other cases. The criticism to be offered here is, first: that they used no controls; and second, 14 of their 37 subjects were given prolactin ranging from one to six days postpartum. Hirst (12) states, "there is found, at the end of the seventh day, about 14 ounces of milk in the 24 hours. During the five preceding days the quantity is small and variable. By the end of the fourth week the quantity of milk secreted in the twenty-four hours reaches about two pints." It is well known that many women have delayed lactation postpartum and that when the flow of milk begins that it is the

usual occurrence for the amount to increase normally with nursing. The clinical evidence for artificial stimulation of lactation in the postpartum woman presented by Kurzrok, et al., is not as convincing as it might be.

### EXPERIMENT TO PRODUCE LACTATION IN CASTRATE GIRLS

The author believes that the ideal human on whom to test the efficacy of prolactin is the castrate woman, having the uterus intact. (However, the possible influence upon lactation of the fetal factor in the pregnant and postpartum woman must be kept in mind.) In this type of patient one can be certain that castration is complete by the absence of menstruation, atrophy of the breasts and genitals, and the presence of subjective symptomotology. With this idea in mind, eight women, ranging in age from 21 to 35 years, who had had this type of operation, were treated as follows: Patients 1 and 2 were given 500 rat units of amniotin (Squibb) in corn oil intramuscularly, every other day, for a period of 45 days, a total of 11,500 rat units, to develop the breasts. Patients 3 and 4 were given the same amount of amniotin in a similar manner, plus 125 rat units of follutein (Squibb) daily intramuscularly (total, 5750 rat units). The reason for this combination of amniotin and follutein is the fact that both of these substances are present in the pregnant woman during gestation, and it was considered interesting to know what effect would be had upon the breasts and the probable relation to lactation. Patients 5 and 6 were given 200 rat units theelin daily intramuscularly for 14 days; 300 rat units theelin for the second 14-day period and 400 rat units theelin the next 18 days. At the end of this time the amount of theelin was decreased to 200 rat units daily for three days. During these last three days 10 rabbit units corporin (Hisaw) was given intramuscularly daily by separate injection and then the 10 rabbit unit dosage of corporin was continued daily alone for another seven-day period.

### INJECTIONS OF PROLACTIN

The day following the cessation of the above described injections patients 2, 3, and 4 were given 200 bird units prolactin intramuscularly daily for a period of 14 days. Patient 1 was given 200 bird units prolactin daily for four days, but complained that the injections were painful, therefore her dosage was decreased to 100 bird units for the next nine injections. During this 14-day period the injections were unavoidably missed on the tenth day in all patients. Patients 2, 3, and 4 received a total of 2600 bird units of prolactin, while patient 1 received 1700 bird units. Patients 5 and 6 were given 200 bird units prolactin intramuscularly on the sixth day following the last injection of corporin. No more prolactin was given to these two patients because of the severe anaphylactic reactioins which followed these initial injections. Patient 5 received 200 bird units prolactin at 1:30 p.m. Within one hour the site of injection became tender, painful, swollen and indurated over an area five inches in diameter. At 9:30 p.m., the head, trunk and extremities began to itch, followed

by intense urticaria which continued for 48 hours. There was marked edema of the face and about the eyes, the tongue was swollen and the larynx became involved so that the voice was very husky. This was partially controlled by 1 cc. adrenalin hypodermically on four occasions, ephedrine 3/8 gr. at intervals and alkaline drinks. Patient 6 was given 200 bird units prolactin intramuscularly into the gluteal region about four inches below the iliac crest at 6 p.m. In about two hours the injection area became painful and began to swell. The swollen area increased in size until at 7 a.m. (13 hours after the injection), it involved the entire right gluteal region, extending to the spine posteriorly, four inches above the right iliac crest and downward to the middle of the thigh. Anteriorly it involved the right groin and the right labium majora and minora, which were extremely edematous and tender. The patient remained in bed for two days and applied ice bags to the swollen area. After 48 hours the reaction began to subside and disappeared in seven days. No rise in temperature accompanied the reaction in patient 5, and patient 6 stated that she did not believe that she had increased bodily temperature. (I did not see patient 6 until at the end of 48 hours. She telephoned, stating "that she had a reaction and that it would not be necessary for me to see her.") I did not realize the extent of the reaction at the time, because of her assuring conversation that there was no reason to be alarmed. Two castrates, patients 7 and 8, were used as controls. These girls did not receive any preliminary injections for breast development. They received daily injections of 200 bird units prolactin for a period of 10 days (one day was missed), a total of 1800 bird units. The eighth injection of prolactin given to patient 8 produced a severe generalized urticarial reaction, with edema about the face. As this was the first reaction that had been experienced from prolactin, and because the patient felt that it was from some food that she had eaten, she was given another injection of prolactin two days later with marked exacerbation of the reaction.

### EFFECT OF THE VARIOUS HORMONES UPON THE BREASTS

Before the onset of injections the breasts of all castrates were soft and flabby, the nipples were flat and the lactiferous ducts atrophied.

*Amniotin.* Amniotin caused the breasts of patients 1 and 2 to enlarge, the nipples erected and the gland trees felt like firm worm-like cords, with a suggestion of slight budding and tingling and itching, especially in nipple areas.

*Amniotin and Follutein.* The breasts of patients 3 and 4 responded as did those of patients 1 and 2, except that they became somewhat larger. A few drops of colostrum-like fluid could be expressed by patient 3 from time to time.

The author wishes to express his thanks to E. R. Squibb & Sons and Dr. J. A. Morrell for the Amniotin, Follutein and Prolactin used; to Parke, Davis & Co., and Dr. E. A. Sharp for the supply of Theelin; to Dr. David Klein of Wilson Laboratories, who furnished the luteal tissue, and to Dr. F. F. Hisaw, who extracted the corporin.

In patieint 4 the areolar areas showed increased pigmentation.

*Theelin and Corporin.* Theelin caused marked enlargement of the breasts of patients 5 and 6, with cord-like enlargement of the gland trees, erection of the nipples, accompanied by tingling, itching in the nipple areas, tenderness and aching. At the ninth day of corporin injections the breasts of patient 5 were larger, felt full and tense and she stated "that she had a sensation of milk trickling down the ducts from the periphery toward the nipples, just as she had experienced previously when she nursed her only baby." On the fourteenth day following onset of corporin injections, which was four days after the cessation of corporin treatment, the breasts had increased greatly in size, were tense and tender, the ducts felt "knotty" as if much budding had occurred and the areolar areas were much darker. The breasts remained in this condition for about two weeks before they began to recede. Within 24 hours after the first injection of corporin, patient 6 noticed increased tenderness of the breasts; manipulating them or movement of the arms was distinctly painful. After the tenth injection of corporin the breasts were markedly enlarged, very tense, stood out firmly, nipples were erected and they were very sensitive to manipulation. The ducts became tortuous and nodular, and there was a drawing sensation extending from the axillae to nipple areas.

*Prolactin.* After the second injection of prolactin in patient 1 the breasts became firmer and more tense and she stated that "there was a burning sensation in the nipples and nipple areas, accompanied by a feeling that milk was trickling down the ducts." On the tenth day after onset of prolactin injections she stated that "the breasts had increased more than twice in size, were very heavy and tense, and felt like lactating." The ducts felt nodular. She did not lactate. Nine days following last injection of prolactin the breasts began to recede slowly.

After the second injection of prolactin in patient 2 she noticed that the breasts were getting larger and more tense and stood out firmly with the nipples erected. After the seventh injection of prolactin, there was a sensation of something trickling in the gland trees from the periphery to the nipples. After the last injection the patient was positive that the glands had enlarged for her brassiere was too tight to be worn. The ducts felt tortuous and nodular. Two weeks after the last injection of prolactin the breasts had not receded. She did not lactate.

Patient 3 noticed that the breasts were more tense and felt heavy and full after the second injection of prolactin. After the sixth injection a few drops of a colostrum-like fluid could be expressed from the breasts and she had a sensation that milk was coming down the ducts. At the twelfth day the breasts felt nodular, had more than doubled in size and she complained of embarrassment because of this. Nine days following the last injection the breasts began to feel less tense. Lactation did not occur.

Following the second injection of prolactin in patient 4 the breasts felt more tense and tender and the nipples were firmer. After the tenth

injection the breasts had increased more than twice in size, felt nodular, stood out more firmly and were very tender. There was a trickling sensation from the periphery toward the nipples. She did not lactate. Eleven days after the last injection, the breasts began to recede.

The one injection of prolactin given to patients 5 and 6 did not have an appreciable effect upon the breasts.

Control patient 7 noticed that the breasts became larger after the sixth injection of prolactin, and her brassiere became too tight. She did not lactate. Control patient 8 noticed that her brassiere, which had been loose, became too tight after the second injection of prolactin. The breasts increased in size and became more tense and tender for about seven days following the last injection, when they began to recede. Lactation did not occur.

## SUMMARY

1. Eight castrate women having their uteri intact, were treated in an experiment to produce lactation. Six of these women were given estrogenic hormones (amniotin or theelin) to develop the breasts. Two of these patients received in addition follutein, and two were given corporin. Following this prolactin was used.

2. All patients who received the estrogenic hormones experienced stimulation and development of the breasts.

3. The combination of amniotin and follutein had a similar effect upon the breasts as did amniotin alone, with the exception that the breasts of the two patients became somewhat larger.

4. Corporin caused a marked increase in the size of the breasts beyond the typical theelin effect. They stood out more firmly and the ducts became more tortuous and nodular, with increased prominence of the nipples, accompanied by a sensation of something trickling down the ducts toward the nipples.

5. The prolactin caused marked enlargement of the breasts with evidence of increase in activity suggestive of impending lactation.

6. Two castrate controls who had not received preliminary injections of ovarian hormones noticed a very appreciable stimulation of the breasts from prolactin alone.

7. None of the women lactated.

8. Prolactin produced a severe anaphylactic reaction in three patients, which is suggestive of the presence of a protein molecule or substance.

## REFERENCES

1. Hildebrandt, P.: Beitr. z. chem. Phys. u. Path. **5**: 463. 1904.
2. Halban, J.: Arch. f. Gynäk. **75**: 352. 1905.
3. Frankl, O.: Am. J. Obst. & Gynec. **6**: 399. 1923.
4. Stricker, P. and F. Grueter: Compt. rend. Soc. de biol. **99**: 1978. 1929; Presse méd. **37**: 1268. 1929.
5. Corner, G. W.: Am. J. Physiol. **95**: 43. 1930.

6. Turner, C. W. and A. H. Frank: Missouri Agricultural Experiment Station Research Bulletin No. 174 (September), 1932.
7. Allen, Edgar: Contrib. Embryol. (No. 98), **19:** 1. 1927.
8. Werner, A. A. and W. D. Collier: J. A. M. A. **100:** 633. 1933; Ibid. **101:** 1466. 1933.
9. Nelson, W. O.: Endocrinology **18:** 1. 1934.
10. Riddle, O., R. W. Bates and S. W. Dykshorn: Am. J. Physiol. **105:** 1. 1933.
Riddle, O. and R. W. Bates: Endocrinology, **17:** 6. 1933.
11. Kurzrok, R., R. W. Bates, O. Riddle and E. G. Miller, Jr.: Endocrinology **18:** 1. 1934.
12. Hirst, B. C: A Text-Book of Obstetrics, W. B. Saunders Co., Philadelphia. 1918.

# ENDOCRINE INTERRELATIONS DURING PREGNANCY

H. SELYE, J. B. COLLIP AND D. L. THOMSON
*From the Department of Biochemistry, McGill University*
MONTREAL

The formation of particularly large corpora lutea during gestation, and the fact that ovariectomy usually interferes with the maintenance of pregnancy, make it very likely that ovarian hormones are of great importance for the developing embryo. It has been shown, however, that in the human and several other species pregnancy may continue even though the ovaries be removed at a relatively early stage of embryonic development. Furthermore, the corpus luteum of gestation involutes in many species long before delivery, and one may therefore be led to believe that the corpus luteum hormone is only necessary for the progestational proliferation of the uterine mucosa preparatory to the nidation of the fertilized ovum. This theory, however, would not explain why in other animals—for instance in the rat—pregnancy is interrupted by ovariectomy even if the ovaries be removed during the last part of gestation. In this communication, we wish to report a series of experiments which may throw some light on the rôle of the corpus luteum hormone, and on the remarkable species differences in the hormonal regulation of pregnancy.

Before we describe our experiments we should like to say a few words about the reaction of the rat uterus to corpus luteum hormone. We have to distinguish between two distinct stages. During the first stage the uterus is not much enlarged, but is hyperaemic and turgid, its surface is rich in venous varicosities protruding above the surface of the organ, giving it a slightly granular appearance. Histologically the uterine epithelium shows many mitotic figures but no cilia and no secretion. The submucosa is well developed, rich in cells, and poor in fibres. This appearance is quite characteristic of early pregnancy, lactation, copulation pseudopregnancy, or of the suckling pseudo-pregnant condition as described in our previous communications (1), and represents the reaction of the rat uterus to such quantities of corpus luteum hormone as are present in the circulation during the conditions mentioned above. We shall refer to it as "the first progestational reaction." The first progestational reaction is readily distinguishable from the oestrus and from the castrate condition, on account of the development and very cellular type of the submucosa. The morphological picture of the organ, particularly the development of the submucosa, suggests that these changes represent a preparation for the nidation of the ovum, but the muscular wall is poorly developed and the organ is fairly rigid at this stage, so that the developing embryo could not distend it sufficiently unless its structure were to change in the later stages of pregnancy. Changes, however, do take place, and in this con-

nection we should like to emphasize the fact that the morphological structure of the rat uterus is entirely different during the first and the second half of the period of gestation. In the second half of pregnancy, the organ is greatly enlarged, bluish in color, and has a smooth surface with no varicosities. The epithelium becomes ciliated; its cells are much larger and higher than during the previous stages, and they begin to secrete. The mucosa forms many folds which protrude into the lumen. The submucosa is poor in cells but rich in fibres; the muscular wall is well developed and easy to distend. The elasticity of the organ facilitates the expansion of the gestation sacs and the secretion of mucus is probably a preparation for delivery. We shall refer to this morphological picture as the "second

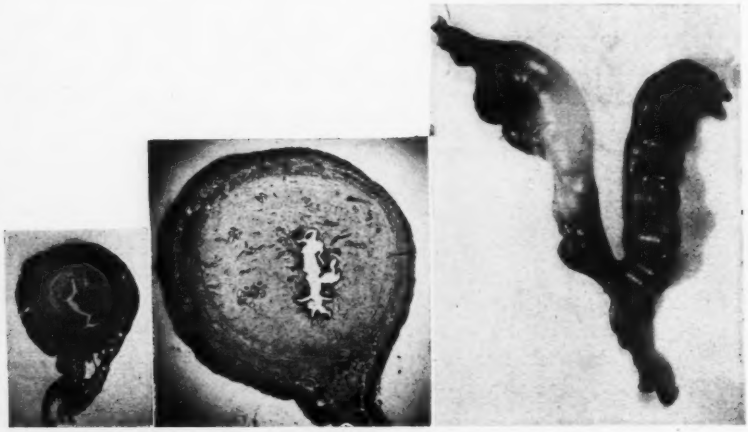


Fig. 1 Fig. 2 Fig. 3

Figure 1. Uterus on 8th day of lactation, showing first progestational reaction. The submucosa are well developed, rich in nuclei and poor in fibers. The structure of the surface epithelium is of relatively simple pattern without lace-like irregularities. The subperimetrial veins are dilated.

Figure 2. Sterile horn of uterus on 19th day of pregnancy, showing second progestational reaction. The submucosa are rich in connective tissue fibers and poor in nuclei. The surface epithelium shows lace-like irregularities.

Figure 3. Uterus of rat 5 days after ovariectomy during first part of gestation. All placentae are alive, but all embryos except one, on left side, are dead. This embryo is obviously under great pressure, and its gestation sac adapts itself to the shape of the involuting uterus.

progestational reaction." It occurs only in the presence of very large quantities of corpus luteum hormone such as are presumably present in the blood stream during the later stages of gestation or after the administration of large quantities of gonadotropic hormone causing marked luteinization of the ovaries. The possibility that this second reaction is not due to corpus luteum hormone alone but to the combined effect of this and other hormones (oestrin?) has to be considered, but at the present time we do not have enough evidence either for or against such an assumption (Figs. 1 and 2).

In our first experiment concerning the effect of ovariectomy in the pregnant rat, six animals were ovariectomized between the ninth and the

twelfth day of pregnancy. None of them aborted, and five days after ovariectomy — when they were sacrificed — the histological examination showed that their placentae were still alive and adherent to the wall of the uterus. The embryos, however, were all dead, except a single embryo in one of the animals (Fig. 3). The gestation sac of this one embryo was elongated, adapting itself to the shape of the uterus, and was obviously under great pressure owing to its inability to distend the uterine wall as the gestation sac normally would. The uterus between the placentae showed the first progestational reaction, although the pregnancy was fairly well advanced by that time. Only in the immediate vicinity of the placentae did we find high secreting cells with indistinct cell membranes lining folds of the submucosa—that is, changes corresponding to the second progestational reaction (Fig. 4).

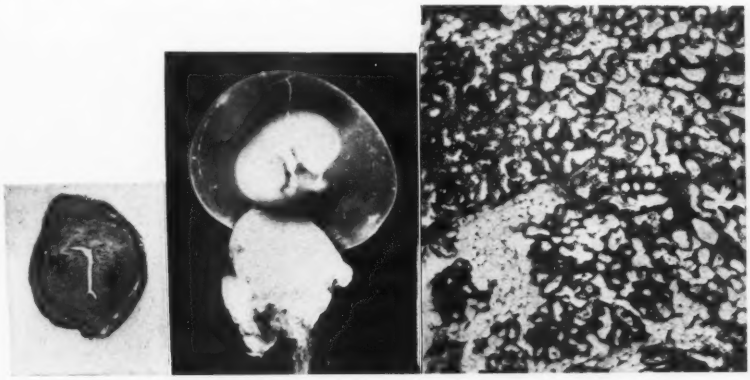


Fig.4 Fig. 5 Fig. 6

Figure 4. Uterus of pregnant rat between two placentae, five days after ovariectomy, showing first progestational reaction. (Compare with Fig. 1.)

Fig. 5. Well-developed foetus in gestation sac, nine days after ovariectomy and transplantation of the embryo into omentum.

Figure 6. Fully developed mammary gland 7 days after removal of ovaries and all foetuses. The placentae were alive.

In four cases we transplanted a whole gestation sac very early during gestation into the omentum and removed the ovaries at the same time. The animals were killed 9 days later; at this time all the embryos were dead. Only one transplantation was successful, and the embryo of this gestation sac, which was inserted outside of the involuting uterus, was the only one that did not die (Fig. 5).

The removal of the ovaries had no effect on the placenta, but it interfered with the development of the second progestational reaction, the relaxation of the uterine wall, and this is probably responsible for the death of the embryos. The histological appearance of the uterus, showing the first progestational reaction, apparently proves, however, that even five days after the removal of the ovaries there must have been corpus luteum hormone in the circulation. Since in the case of the removal of the ovaries dur-

ing pseudopregnancy the first phase of progestational reaction invariably disappears within 48 hours, and since on the other hand, Caesarian section is followed by full oestrus (''post-partum oestrus'') after the same length of time—unless the ovaries be removed together with the gestation sacs, in which case the uterine mucosa would show marked involution at this period—we thought that the placenta might possibly also produce progestin, which in the non-pregnant condition is produced by the corpus luteum only.

The bulk of the evidence at the present time does not seem to be in accord with such an assumption. Thus Westman (2) states that the placenta cannot produce corpus luteum hormone because the gestational proliferation retrogresses in the mucosa of the sterile horn of the unilaterally pregnant rabbit after cauterization of the corpora lutea. But since all of his animals aborted on the first or second day after ovariectomy they have little significance for this argument. Furthermore, Philipp (3) tried in vain to produce progestational changes in the uteri of ovariectomized rabbits with implants of human placenta. He concludes, therefore, that the placenta contains no corpus luteum hormone and that it may influence the uterus only indirectly, by stimulating the hormone production of the ovary. Similarly Corner and Allen (4) and later Fels (5) were unable to obtain corpus luteum hormone from placental tissue with the methods used for the preparation of this hormone from corpora lutea. The latter author concludes, nevertheless, that the placenta produces corpus luteum hormone, since the relaxation of the pelvic ligaments will occur in spite of ovariectomy in the pregnant guinea pig. This argument, however, loses its value in the light of more recent findings [Brouha (6) and others] showing that this reaction is not characteristic of corpus luteum hormone, but may also be obtained with oestrin. The same criticism applies to the work of Shugo, et al (7), who obtained extracts from human placenta which lead to relaxation of the pelvic ligaments and development of the mammary glands in the castrate female guinea pig. Since both these reactions may be obtained with oestrin, they do not prove the presence of corpus luteum hormone in the placenta.

The only finding that seems to lend some support to the theory mentioned above is that of Adler, Fremery and Tausk (8), who prepared extracts from human and cattle placenta which produced progestational changes in the uterine mucosa of the infantile rabbit. It is very likely, therefore, that they really obtained corpus luteum hormone, and even though the equivalent of 500-1500 gm. of placental tissue was needed in order to produce a positive reaction, it might be that the placenta contains more of this principle than can be extracted with the method used. Ehrhardt (9) has also obtained corpus luteum hormone from the placenta. Of course, the presence of corpus luteum hormone in the placenta would still not prove that it has been produced there, just as the presence of oestrin in the embryo does not prove the production of this hormone by the foetal tissue.

The observation that ovariectomy is compatible with the continuation of pregnancy in some species may also be considered as proof of the formation of corpus luteum hormone by the placenta or the embryo. This, however, is usually possible only during the later stages of gestation when the corpora lutea begin to involute and their hormone may no longer be necessary. Furthermore, since in many species (for instance, in the rat) ovariectomy invariably terminates gestation, and since even in those species in which the removal of the ovaries is compatible with the maintenance of pregnancy this is the case in only a certain percentage of the cases, it is very difficult to evaluate these findings. In addition to these objections, one can never eliminate the possibility of a species predisposition for the formation of accessory ovarian tissue, a species difference in the need of the ovum for corpus luteum hormone, and so forth. It seemed to us that the question will never be solved unless one can demonstrate formation of

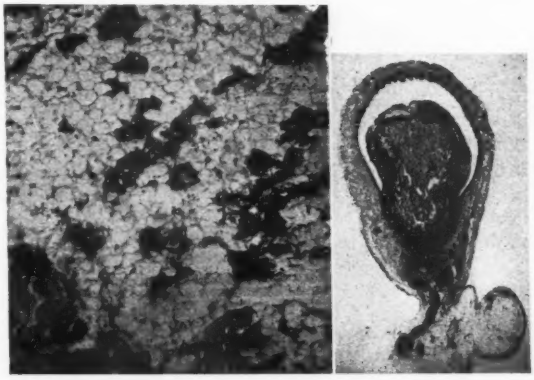


Fig. 7 Fig. 8

Figure 7. Atrophic mammary gland 7 days after removal of ovaries, foetuses and placentae.

Figure 8. Section through living placenta five days after removal of ovaries and all foetuses. Note irregularities of uterine wall in antimesometrial region.

corpus luteum hormone in the organism of an ovariectomized pregnant animal belonging to a species in which the corpora lutea remain functional during the entire length of gestation, and in which ovariectomy is known to terminate pregnancy in all stages.

The experiments mentioned in the first section of this communication have shown already that in the rat ovariectomy during early pregnancy will not interfere with the life of the placenta, even though the foetus dies. We therefore decided to remove both the ovaries and all the embryos, so as to obtain an experimental arrangement which will leave no doubt as to the origin of the corpus luteum hormone, if any can be demonstrated, eliminating the possibility of the liberation of corpus luteum hormone from decomposing foetal tissue. We particularly wanted to eliminate this point on account of the publications of Lane-Claypon and Starling (10), Biedl and

Königstein (11), Hammond (12) and others, who stated that the foetus produces substances which control the activity of the mammary gland.

In six rats both ovaries and all the embryos were removed at approximately the middle of pregnancy, leaving the placentae intact. The animals were sacrificed 5-9 days later. At this period the placentae were still alive, the uterus between the placentae showed the first progestational reaction, and the mammary glands—which in the rat invariably begin to secrete 30-40 hours after Caesarian section and then involute rapidly if not nursed —were well developed. Milk was present in the acini and galactophores in most cases. The foetal vessels of the placentae were obliterated but the syncytium, the foetal giant cells, and the small and large cellular trophoblast were all well preserved (Figs. 6, 7, 8 and 9).

We feel that these experiments suggest that progestin may be produced by the placenta.

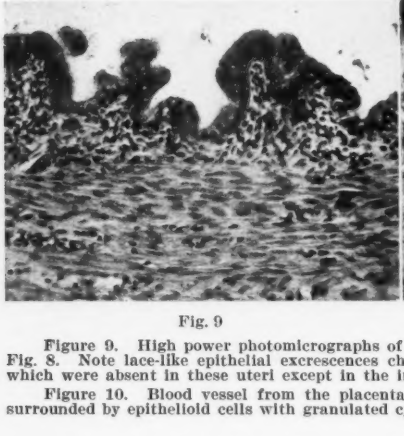


Fig. 9

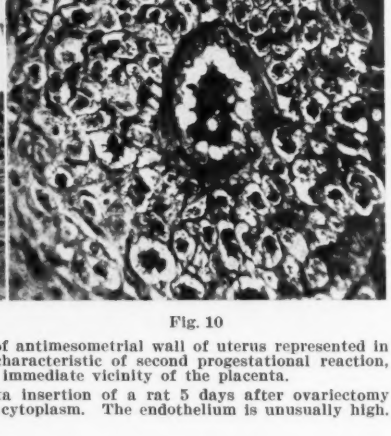


Fig. 10

Figure 9. High power photomicrographs of antimesometrial wall of uterus represented in Fig. 8. Note lace-like epithelial excrescences characteristic of second progestational reaction, which were absent in these uteri except in the immediate vicinity of the placenta.

Figure 10. Blood vessel from the placenta insertion of a rat 5 days after ovariectomy surrounded by epithelioid cells with granulated cytoplasm. The endothelium is unusually high.

Our previous experiments (13) convinced us that the maintenance of the corpora lutea of gestation cannot entirely be explained by the action of the known gonadotropic hormones in themselves, and that some other factor must be present during this period in order to produce the ovarian structure typical of pregnancy. Since it has been found that hypophysectomy during the second half of gestation does not influence the histological appearance of the corpora lutea and mammary glands in rats (14) and mice (15), we assumed that the stimulus necessary for their maintenance must come from the pregnant uterus, but we did not know whether it comes from the foetus or the placenta. Since the experiments reported in the first part of this communication showed that the placenta may survive the embryo for a considerable length of time in ovariectomized rats, we wished to see how long the placenta would live after the surgical removal

of the embryo, and whether the corpora lutea and the mammary glands of such animals, with placentae but no embryos, would be the same as those of normal gestation.

The fact that the placenta may survive the embryo for a short time is well known from clinical observations. This question, however, has not received much attention from experimental physiologists. The only species on which such experiments have been performed is the rabbit, of which Weymeersch (16) said that the placenta does not die immediately after ovariectomy, but the results obtained later were somewhat contradictory. Hammond (12) removed the foetuses from six rabbits between the 13th and 15th day of gestation, and found that the placentae became atrophic, and the mammary glands ceased to grow. Still more recently, Klein (17) confirmed and extended the findings of Weymeersch, but since he killed his animals within five days of ovariectomy his experiments do not decide whether the factor determining the length of gestation is in the foetus or in the placenta, and whether the latter is entirely independent of the former. Encouraged by the observations on rats described above, and feeling also that such experiments would be more interesting in a species in which the presence of the ovary is essential during the entire period of gestation, we repeated these experiments on twelve rats between the 9th and 13th day of gestation. Since we found that when larger incisions are made the placentae are often delivered into the peritoneal cavity, the embryos were removed by pressure through a very small incision made with the point of a cutting-edge needle. We found that in these animals the mammary gland was maintained in a well-developed, non-lactating condition; the vagina remained dioestric; the uterus showed varying degrees of progestational changes; and the corpora lutea of pregnancy were maintained for a period of about 8 to 12 days, at the end of which period the placentae were aborted, and milk secretion began. This means that the length of pregnancy (which is normally 21 days in the rat) was not considerably altered by the removal of the embryo. We think that these experiments justify the conclusion that the placenta determines the length of pregnancy either by its effect on the corpora lutea, or by its own progestin production, or—which is more likely—by both these means.

Since these experiments suggest that the placenta may produce ovarian hormones, the involution of the ovary during gestation might be looked upon as an inactivity atrophy. This assumption would be in accordance with the fact that pregnancy is particularly independent of the ovary in such species as the human, in which the corpus luteum involutes very early during gestation. The possibility that the placenta would need the same hormonal stimuli for the production of ovarian hormones as does the ovary, has to be considered since it might throw some light on the reasons for the massive production of such substances during gestation. Since hypophysectomy does not interfere with the maintenance of gestation in the rat, these gonadotropic substances would, of course, have to be produced by the placenta itself.

According to several investigators (18) the epithelioid cells found in the uterine wall just below the placenta have an endocrine function. We have observed, in preliminary experiments, that these cells, whatever their function may be, are largely independent of the placenta, for they remain in a fully developed condition several days after the placenta has been removed. They also seem to be largely independent of the gonad, since ovariectomy does not cause their immediate involution (Fig. 10). Since, on the other hand, they disappear immediately after delivery, it is reasonable to assume that they are of some importance during the period of gestation. We wish to report elsewhere on the morphology and physiology of these cells in detail; we mention them here only because of the rôle which they might possibly play in the endocrine correlations during pregnancy.

## SUMMARY AND CONCLUSIONS

1. In the rat ovariectomy during gestation was found not to interfere with the life of the placenta. It terminates pregnancy only because it causes the death of the foetus; and the dead foetus, if it is large enough at the time of the intervention, will cause the abortion of the whole gestation sac, simply acting as a foreign body. The probable cause of the death of the foetus is the partial involution of the uterus which considerably increases the pressure in the gestation sac.

2. The placenta of the rat must produce corpus luteum hormone, since the uterus was found to show distinct progestational changes, and the mammary gland to be maintained in a well-developed condition for as long as six days after the simultaneous removal of the ovaries and all the embryos.

3. The placenta survived in apparent functional integrity after removal of the ovaries and the foetuses, hence is independent of ovarian hormones even in the rat, a species in which ovariectomy invariably terminates gestation. There is probaly no species difference in this respect, and whether pregnancy is or is not interrupted is determined merely by incidental facts—namely, by the resistance of the embryo to such pressures as will be occasioned by ovariectomy in the uterus, and by the degree to which the production of ovarian hormones has been transferred into the placenta.

4. Since the life-span of the placenta was not markedly influenced by the removal of the embryos, the length of the gestation period must be determined by factors inherent in the placenta.

## REFERENCES

1. Selye, H. and T. McKeown: Proc. Soc. Exper. Biol. & Med. **31:** 683. 1934.
Selye, H. and T. McKeown: Anat. Rec. **60:** 323. 1934.
2. Westman, A.: Acta obst. et gynec. Scandinav. **10:** 420. 1930.
3. Philipp, E.: Zentralbl. f. Gynäk. **54:** 2754. 1930.
4. Corner, G. W. and W. M. Allen: Am. J. Physiol. **88:** 326. 1929.
5. Fels, E.: Zentralbl. f. Gynäk. **55:** 514. 1931.
6. Brouha, L.: Compt. rend. Soc. de biol. **113:** 406. 1933.
7. Shuga, K., K. Fujimoto and F. Takeda: Mitt. d. Jap. Ges. f. Gynaekol. **27:** 30. 1932.
8. Adler, A. A., P. de Fremery and M. Tausk: Nature, London, **133:** 293. 1934.

9. Ehrhardt, K.: München. med. Wchnschr. **81:** 869. 1934.
10. Lane-Claypon, J. and E. H. Starling: Proc. Roy. Soc. **(B) 77:** 505. 1906.
11. Biedl, A. and R. Königstein: Ztschr. f. exper. Pathol. u. Therap. **8:** 2. 1910.
12. Hammond, J.: Proc. Roy. Soc. **(B) 89:** 534. 1917.
13. Selye, H., J. B. Collip and D. L. Thomson: Anat. Rec. **58:** 139. 1934.
Selye, H.: Proc. Soc. Exper. Biol. & Med. **31:** 488. 1934.
14. Selye, H., J. B. Collip and D. L. Thomson: Proc. Soc. Exper. Biol. & Med. **30:** 589. 1933.
15. Selye, H., J. B. Collip and D. L. Thomson: Proc. Soc. Exper. Biol. & Med. **31:** 82. 1933.
16. Weymeersch, A.: Ann. et bull. Soc. roy. d. Sc. méd. et nat. de Bruxelles, **70:** 104. 1912.
17. Klein, M.: Arch. d'anat., d'histol. et d'embryol. **18:** 1. 1934.
18. For references see: Grosser, O. Frühentwicklung, Eihautbildung und Placentation-München, J. F. Bergmann. 1927.

# CHANGES IN THE ANTERIOR HYPOPHYSIS OF THE MALE ALBINO RAT AFTER CASTRATION AND EXPERIMENTAL CRYPTORCHISM*

E. T. ELLISON† AND J. M. WOLFE
*The Department of Anatomy*
*Vanderbilt University School of Medicine*
NASHVILLE, TENNESSEE

In previous communications (Ellison and Wolfe, 1934 and 1935,‡ and Wolfe, 1934) we described the changes in the anterior hypophysis of the female rat occurring after castration. In this paper we wish to present similar studies carried out on male albino rats. Since it has frequently been stated in the literature that cryptorchism in the male rat results in changes in the anterior lobe suggestive of those of castration, we have compared the anterior lobes of castrated and cryptorchid males, sacrificed at equal time intervals after operation (either castration or abdominal suspension of the testes). Since we (Ellison and Wolfe, 1934) have previously reviewed the literature pertaining to castration in both male and female rats, it will be necessary to mention only a few papers pertinent to the subject considered here.

It is generally agreed by many investigators that castration in the male rat leads to an increase in the size of the gland and that histologically there is an increase in the number and the size of the basophilic cells leading to the formation of castration cells. These studies have recently been reviewed by Stein (1933). Zacherl (1912) and Schleidt (1914) report an increase in the eosinophiles, while Addison (1917) and Severinghaus (1933) state that there is a decrease of the eosinophiles.

In cryptorchid rats, Moore (1924) has described rapid and almost complete destruction of the germinal epithelium within 20 to 30 days after abdominal suspension of the testes. The accessory reproductive organs were normal. Evans and Simpson (1929) found that the anterior lobes of cryptorchid males contained amounts of the gonad-stimulating complex intermediate between those found in the anterior pituitaries in normal and castrated males. Martins and Rocha (1931) reported that the anterior lobes of cryptorchid males are castrate in type. Van Wagenen (1925) and Nelson (1933) have reported that the anterior lobes of male rats deprived of vitamin E (and consequently suffering a destruction of the germinal epithelium) exhibited certain changes simulating those of castration.

*These studies have been supported by grants from the Committee for Scientific Research of the American Medical Association and the Division of Medical Science of the Rockefeller Foundation.

†Mr. Ellison's participation in these studies was made possible by a grant from the Henry Strong Denison Foundation.

‡In this paper (Ellison and Wolfe, 1935) the eosinophiles, the basophiles and the cromophobes were listed as cells of type I, III and IV, respectively. This special terminology for the anterior lobe cells has since been discontinued and in the present paper the more generally used terminology for the various cell types has been adopted.

More recently several abstracts have appeared concerning changes in the anterior lobes of male rats after castration and cryptorchism. Nelson (1934) reported a basophilic increase and vacuolization of these cells. In long-term cryptorchids there was atrophy of the seminal vesicles. Parkes (1934) reported retarded castration changes in cryptorchid males. By 16 weeks, however, there were equal numbers of basophiles in the castrates and cryptorchids, but far less vacuolization of the basophiles in the cryptorchids. In the same group of abstracts, Ellison and Wolfe (1934) presented a brief report of the studies to be discussed in this paper.

## MATERIALS AND METHODS

All animals used were adult albino male rats, weighing at least 150 grams at the beginning of the period of study. A control group of 42 rats was allowed to reach various weights up to 430 grams and were sacrificed. A second group of 41 rats was castrated and members of this group were sacrificed at 15, 55, 120 and 180 days after operation. In a third group of 34 rats the testes were brought up through the inguinal canal and sutured to the lateral abdominal wall. These were later sacrificed at intervals corresponding to those in the castration series. Observations on all animals included body, pituitary, prostate and seminal vesicle weights, and testis weights, except in the castrate series. The testes and accessory reproductive organs were fixed in Bouin's fluid and stained in hematoxylin and eosin. The pituitaries were prepared for study by methods already described (Cleveland and Wolfe, 1932). In order to express the pituitary weight in terms of body weight a factor was derived:

$$\frac{\text{Pituitary Weight (in mg.)}}{\text{Body Weight (in gm.)}} \times 1000 = \text{Pituitary Factor}$$

All pituitaries were studied from a morphologic and quantitative basis, as has been described fully in previous publications. Cell counts were made on all pituitaries included in this series (see Table 1). In order to facilitate interpretation of the results, the data have been interpreted by statistical methods. In Table 1 a frequency distribution analysis is presented; this table gives the total number of animals used in each group and the range of the percentage of the various cell types present in each group. In Table 2 the summaries of each group are given, including the arithmetic mean and the standard deviation.

*Anterior Hypophyses and Sex Organs of Normal Male Rats.* The pituitaries of normal male rats, when observed before removal from the sella, appeared definitely smaller than those of normal females described previously, and after weighing and calculating the mean pituitary factor, it was found to be 2.7 as against 4.5 for the normal female. The mean testis weight, when compared with Donaldson's standard weights (1924) for normal males, was 105 per cent normal. The mean of the prostate and seminal vesicle weights was 2.2 grams (weighed together). These com-

TABLE 1

QUANTITATIVE DATA FROM NORMAL, CASTRATED AND CRYPTORCHID MALE RATS ARE PRESENTED IN THE FORM OF A FREQUENCY DISTRIBUTION TABLE. THE LEVELS OF THE VARIOUS CELL TYPES PRESENT IN THE DIFFERENT GROUPS ARE SHOWN

| Percentage of Cell Types | Normal | Castrates | | | | Cryptorchids | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 15-day | 55-day | 120-day | 180-day | 15-day | 55-day | 120-day | 180-day |
| Eosinophiles: | | | | | | | | | |
| 35.0–39.9 | 1 | .. | 1 | 2 | .. | .. | 1 | .. | .. |
| 40.0–44.9 | 5 | 2 | 3 | 2 | 5 | .. | 3 | 2 | 1 |
| 45.0–49.9 | 13 | 5 | 5 | 7 | 3 | 3 | 5 | 4 | 6 |
| 50.0–54.9 | 14 | 1 | 1 | 2 | .. | 4 | 3 | 3 | 1 |
| 55.0–59.9 | 5 | 1 | .. | 1 | .. | .. | 1 | .. | 1 |
| 60.0–64.9 | 4 | .. | .. | .. | .. | .. | .. | 1 | .. |
| Basophiles: | | | | | | | | | |
| 2.0– 3.9 | 4 | .. | .. | .. | .. | .. | .. | .. | .. |
| 4.0– 5.9 | 15 | .. | .. | .. | 3 | 3 | .. | .. | 3 |
| 6.0– 7.9 | 19 | .. | .. | 2 | 2 | 1 | 1 | 4 | 1 |
| 8.0– 9.9 | 4 | 2 | .. | 6 | 2 | 2 | 4 | 2 | 3 |
| 10.0–11.9 | .. | 2 | .. | 1 | 1 | 1 | 6 | 2 | 1 |
| 12.0–13.9 | .. | 5 | 1 | 2 | .. | .. | 2 | 2 | 1 |
| 14.0–15.9 | .. | .. | 2 | 2 | .. | .. | .. | .. | .. |
| 16.0–17.9 | .. | .. | 4 | .. | .. | .. | .. | .. | .. |
| 18.0–19.9 | .. | .. | 2 | 1 | .. | .. | .. | .. | .. |
| 20.0–21.9 | .. | .. | 1 | .. | .. | .. | .. | .. | .. |
| Castration Cells: | | | | | | | | | |
| 1.0– 1.9 | 5 | 9 | 5 | 1 | .. | 7 | 13 | 9 | 5 |
| 2.0– 3.9 | .. | .. | 5 | .. | .. | .. | .. | 1 | 2 |
| 4.0– 5.9 | .. | .. | .. | 1 | .. | .. | .. | .. | 1 |
| 6.0– 7.9 | .. | .. | .. | 1 | .. | .. | .. | .. | 1 |
| 8.0– 9.9 | .. | .. | .. | 7 | 3 | .. | .. | .. | .. |
| 10.0–11.9 | .. | .. | .. | .. | 1 | .. | .. | .. | .. |
| 12.0–13.9 | .. | .. | .. | 1 | 4 | .. | .. | .. | .. |
| 14.0–15.9 | .. | .. | .. | 2 | .. | .. | .. | .. | .. |
| 16.0–17.9 | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| 18.0–19.9 | .. | .. | .. | 1 | .. | .. | .. | .. | .. |
| Chromophobes: | | | | | | | | | |
| 25.0–29.9 | .. | .. | .. | 7 | .. | .. | .. | 1 | .. |
| 30.0–34.9 | 6 | 1 | 5 | 1 | .. | .. | 2 | .. | 1 |
| 35.0–39.9 | 8 | 1 | 4 | 5 | 7 | 1 | 3 | 4 | 1 |
| 40.0–44.9 | 10 | 5 | 1 | .. | 1 | 4 | 3 | 4 | 5 |
| 45.0–49.9 | 12 | 2 | .. | 1 | .. | 2 | 4 | .. | 2 |
| 50.0–54.9 | 6 | .. | .. | .. | .. | .. | 1 | 1 | .. |
| Total Rats in each group..... | 42 | 9 | 10 | 14 | 8 | 7 | 13 | 10 | 9 |

pared favorably with other prostate and seminal vesicle weights accumulated in this laboratory and were considered normal.

From the morphologic standpoint the pituitaries of the control male rats were similar to those found in normal females, but certain important morphologic and quantitative differences stood out which have already been described (Wolfe and Ellison, 1934). In the male rat both the eosinophiles and basophiles were more abundant and their granular content was greater than in the female. Reference to Table 1 will show that the level of the eosinophiles in the anterior pituitaries of the 42 normal male rats varied from 35 to 65 per cent but that in 27 of these animals the level of these cells was between 45 and 55 per cent. The mean level was 51.2 per cent with a standard deviation of 5.2 (see Table 2).

The basophiles were usually packed with granular material, although a certain number of these cells in the majority of the glands studied exhibited a reduction of granules. A few cells were swollen and entirely devoid of granular material. As pointed out previously (Wolfe and Elli-

## TABLE 2

A SUMMARY OF THE ARITHMETIC MEANS AND STANDARD DEVIATIONS (SD) OF THE NORMAL AND VARIOUS EXPERIMENTAL GROUPS ARE PRESENTED

| Type of Rat | No. of Rats | Animal Weight Gms. | Pituitary Weight Mgms. | Pituitary Factor | Testis Weight Gms. | Testis Weight Per Cent Normal | Prostate and Seminal Vesicle Weight Gms. | Percentage of Cell Types | | | | Cells Counted |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Eosinophiles | Basophiles | Castration Cells | Chromophobes | |
| Normal | 42 | 309<br>SD 72 | 7.5<br>SD 1.7 | 2.7<br>SD 0.3 | 2.64<br>SD 0.5 | .....<br>SD 1.2 | 2.2<br>SD 1.2 | 51.2<br>SD 5.2 | 5.5<br>SD 0.6 | .....<br>SD ..... | 42.2<br>SD 5.7 | 95,550 |
| Castrates: 15-day | 9 | 249<br>SD 40 | 7.7<br>SD 0.9 | 2.8<br>SD 0.4 | ..... | ..... | ..... | 46.7<br>SD 4.6 | 11.3<br>SD 2.1 | 0.2<br>SD ..... | 41.0<br>SD 4.9 | 19,209 |
| 55-day | 10 | 272<br>SD 29 | 9.3<br>SD 2.2 | 3.4<br>SD 0.1 | ..... | ..... | ..... | 45.6<br>SD 3.7 | 17.0<br>SD 1.5 | 1.4<br>SD 0.7 | 35.5<br>SD 3.8 | 29,258 |
| 120-day | 14 | 300<br>SD 52 | 11.8<br>SD 0.9 | 4.1<br>SD 0.8 | ..... | ..... | ..... | 46.0<br>SD 4.6 | 10.6<br>SD 3.9 | 10.4<br>SD 2.5 | 30.5<br>SD 4.7 | 33,878 |
| 180-day | 8 | 368<br>SD 49 | 13.0<br>SD 2.3 | 3.6<br>SD 0.9 | ..... | ..... | ..... | 42.5<br>SD 2.1 | 7.0<br>SD 1.8 | 9.5<br>SD 1.9 | 37.0<br>SD 3.1 | 19,471 |
| Cryptorchid: 15-day | 7 | 262<br>SD 28 | 7.1<br>SD 1.1 | 2.8<br>SD 0.3 | 11.4<br>SD 0.3 | 45.0<br>SD 9 | ..... | 48.6<br>SD 3.4 | 6.9<br>SD 1.8 | 0.1<br>SD ..... | 41.1<br>SD 2.5 | 16,499 |
| 55-day | 13 | 314<br>SD 25 | 8.2<br>SD 1.1 | 2.6<br>SD 0.3 | 1.39<br>SD 0.3 | 47.0<br>SD 8 | ..... | 48.5<br>SD 4.4 | 8.7<br>SD 1.9 | 0.5<br>SD 0.5 | 42.0<br>SD 1.6 | 38,320 |
| 120-day | 10 | 308<br>SD 40 | 9.1<br>SD 0.7 | 3.0<br>SD 0.3 | 1.0<br>SD 0.2 | 37.0<br>SD 9 | 2.02<br>SD 0.44 | 50.4<br>SD 5.6 | 9.2<br>SD 0.9 | 1.1<br>SD 0.8 | 40.0<br>SD 4.4 | 25,280 |
| 180-day | 9 | 356<br>SD 38 | 9.1<br>SD 1.1 | 2.6<br>SD 0.4 | 1.0<br>SD 0.3 | 34.0<br>SD 3 | 2.1<br>SD 0.16 | 48.2<br>SD 4.3 | 8.1<br>SD 2.7 | 2.8<br>SD 1.9 | 42.4<br>SD 4.1 | 21,215 |
| Total Rats | 122 | | | | | | | | | | Total Cells | 298,680 |

son, 1934), the basophiles are larger and more abundant in male rats than in females; the number of cells showing granular loss, in males, was never great. The most striking feature was the presence of a few castration cells in many of the normal glands. Although there were typical signet-ring castration cells, they were never very large. The mean level of the basophiles was 5.5 per cent, with a standard deviation of only 0.6 per cent (Table 2). Table 1 shows that in 34 rats the level of these cells was between 4.0 and 7.9 per cent.

The chromophobes were essentially similar to those found in the female rat; however, they were much less abundant. See Table 1 for distribution and Table 2 for mean percentage and standard deviation. Colloid was found in the clefts in six of these glands, and in eighteen glands mitoses were observed in routine counting. Histologically, the testes, prostates and seminal vesicles were normal.

*Anterior Hypophyses and Sex Organs of the Male Rat After Castration.* This series, comprising 41 rats, was sacrificed at 15, 55, 120 and 180 days after gonadectomy. These animals showed a rather marked progressive increase in the relative weight of the pituitary up to 120 days after castration and then a slight decline (see Table 2). The prostate and seminal vesicles at the end of the 15-day castration period were extremely atrophied; weights were not obtained.

Tables 1 and 2 show a rapid and progressive increase of the percentage of the basophiles through the 55th day of castration, and a less evident increase of the castration cells. Table 1 shows that variation in the cells among the different animals was remarkably small. Following this period (55-day) and clearly indicated in the 120 and 180-day castrates, there was a rather marked decline in the percentage of the basophiles, and a proportionately marked increase in the percentage of the castration cells. Variations in the individual animals were somewhat greater than in the 15 and 55-day castrates (see Table 1). In this table it is seen that the level of the castration cells is slightly lower in the 180-day castrates than in the 120-day castrates.

Throughout the castration period the basophiles showed an increase in staining capacity and in the size of both the cells and their granules and, at the end of the 55-day castration period, almost all of the cells were quite large and packed with granules. Those on the periphery of the gland were usually smaller, although they were densely packed with granules. In the 120 and 180-day groups there was a large number of signet-ring castration cells. The basophiles were large; a few showed clumping of granules and others many small clear vacuoles resembling the "spongy" basophilic cells found in castrated females (Ellison and Wolfe, 1934).

In rats castrated for 180 days the castration cells were very large. Many of these cells exhibited a partial disappearance of colloid from the large colloid-filled vacuoles. The result was a "hole" left in the colloid vacuole of the castration cell. Such changes were interpreted as regres-

sive and, for lack of a better term, we have designated them as "secondary vacuolization." This so-called "secondary vacuolization" was not as marked in the male castrates as it was in the females, and it is discussed more fully in a previous publication (Ellison and Wolfe, 1934).

The mean level of the eosinophiles was slightly decreased throughout the different periods of castration. The mean of these cells in normal males was 51.2 per cent, while that in 180-day castrates was decreased to 42.5 per cent. There were intermediate variants. However, reference to Table 1 will show that the level of these cells found in the 180-day castrates was not below the lower limits of normal for normal male rats. Morphologically the eosinophiles found in the anterior pituitaries of the castrates did not vary definitely from those found in normal males. In some few of the castrate glands there was a slight decrease in granular content and a few of the cells were smaller, but these changes were markedly inconsistent.

Colloid in the residual cleft was found in approximately one-third of the rats castrated for 15 and 55 days and in practically all of those castrated for 120 or 180 days. Mitoses were observed in practically all glands studied but were few in number. Most mitoses occurred in the chromophobes; a lesser number in the eosinophiles. Mitoses were not observed in the basophiles.

*Anterior Hypophyses and Sex Organs of Animals Subjected to Abdominal Suspension of the Testes.* Quantitative data on this group of rats are presented in Tables 1 and 2. Table 2 shows that the pituitaries of cryptorchid rats were not increased in size. The pituitary factors were not markedly changed from 2.7, the mean factor for normal males. The testes of these animals atrophied markedly in the first 15 days after abdominal suspension; the average weight was 45 per cent of the normal (Donaldson's standard used). In the longer term cryptorchids the testis weights were further decreased.

Histologically, these testes presented a marked degeneration of the germinal epithelium, only the basal germinal cells and the Sertoli cells remained intact. At autopsy the prostate and the seminal vesicles appeared normal in size; however, we obtained weights on these organs only in the 120 and 180-day cryptorchids (see Table 2). Compared with our data for normal rats there was only a very slight decrease in weight.

Histological examination of the anterior lobe and cell counts revealed that the level of the eosinophiles varied only slightly from the level found in normal rats, regardless of the period of time elapsing after abdominal suspension of the testes. Morphologically we were unable to detect any changes in the eosinophiles.

The basophiles showed a very mild increase in relative percentages. They increased from a mean level of 5.5 per cent in normal males to a mean level of 9.2 in the 120-day cryptorchid rats, while in the 15 and 55-day cryptorchid rats the levels of these cells were intermediate between

these two extremes (see Table 2). The castration cells began to increase in relative percentage at 100 days, changing from 0.3 per cent normally to 1.1 per cent at 100 days and 2.7 per cent at 180 days. Morphologically the basophiles found in the cryptorchid rats were only slightly larger than those found in normal males. These were well filled with granules.

The castration cells were of the signet-ring type but, on the whole, they were small and few were as large as those found in the castrated rats. Colloid was found in the cleft in only a few instances. Mitotic figures were found in approximately one-half of the glands studied.

## DISCUSSION

Comparison of these studies and those made earlier in this laboratory indicate that, while the anterior lobe of the male rat is basically similar to that of the female, it varies from that of the female in the percentage of the various cell types and in the granular content of these cells. Cell counts were made on 69 female rats (Wolfe and Cleveland, 1934, and unpublished data) killed at the various phases of the oestral cycle; the mean level of the eosinophiles was 33.6 per cent; of the basophiles, 4.8 per cent; and of the chromophobes, 61.9 per cent. Comparison with those for male rats in Table 1 (this paper) shows that the eosinophiles and basophiles are significantly more abundant in the anterior lobes of the males, while the level of the chromophobes is decreased. Morphologically, both granular types in the males are larger and contain more granules, which have a greater affinity for their respective stains than do similar cells in the females.

It is of further interest to compare the effect of castration in the male and female rats. The basophiles increase at about the same rate, although an exact comparison is impossible because the rats were sacrificed at different intervals after castration. However, in both males and females there was a rapid initial rise of the basophiles and then considerably later a rise of the castration cells correlated with the decrease in the basophiles. In each series it seemed definite that the castration cells were modified basophiles, confirming results of many previous investigators.

Changes in the eosinophiles after castration in both males and females are difficult to analyze. We have reported in a recent paper (Wolfe, 1934) that the mean level of the eosinophiles in 69 normal female rats was 33.6 per cent, with a standard deviation of 4.3, while in 39 female rats castrated for 30 days the mean level of these same cells was 41.2 per cent. This would indicate that there was some increase in these cells in females after castration. However, it was pointed out that in normal rats in a few instances the level of the eosinophiles might be slightly higher than 40 per cent. Results published in this paper indicate that there might be a slight drop in the eosinophiles in the male rat after castration, but again the drop is not below the lower limits of normal for non-castrated male rats. It is, of course, difficult to compare the pituitaries of male and female rats because the normal level of the eosinophiles in males is, on an

average, about 15 per cent greater. Changes in the eosinophiles after castration are obscure and no definite conclusion can possibly be reached from our material.

Comparison of the effects of castration and cryptorchism in male rats reveals that cryptorchism results in a mild castration reaction as far as the basophilic elements of the pituitary are concerned. However, in animals cryptorchid for 180 days the anterior lobe reaction failed to attain a castrate condition. Just why a cryptorchid state induces any castration changes in the anterior hypophysis is at present obscure. Martins and Rocha (1931) have suggested that the germinal epithelium secretes a second testicular hormone and by removing the germinal epithelium a restricting force on the anterior lobe is removed. Nelson (1933), using rats deprived of vitamin E, suggests the possibility that in rats deprived of the germinal epithelium, the secretion of the hormone of the interstitial cells is lowered slightly, so that, while the level is high enough to keep the accessory reproductive organs in an approximately normal condition, the level is sufficiently lowered to reduce to a certain extent the depressing factor that the testicular hormone is known to exert on the anterior lobe. Nelson's suggestion is strengthened by the fact that later studies on the seminal vesicles of long-term cryptorchid rats indicate a lowered level of the testicular hormone. Reference to Table 1 shows that the level of the eosinophiles in the anterior lobe of the cryptorchid rats did not vary from the normal.

## SUMMARY AND CONCLUSIONS

1. The anterior pituitaries of 41 male rats castrated for periods varying from 15 to 180 days and of 39 cryptorchid rats, sacrificed at intervals of 15 to 180 days after abdominal suspension of the testes were compared histologically with those of 42 normal male rats. Cell counts were made on representative sections of all glands studied.

2. Castration in male rats led to an increase in the relative pituitary size and a marked increase in the basophilic cells which reached a mean level of 17.1 per cent in the 55-day castrates. At this period signet-ring castration cells first appeared in appreciable numbers. From this time through the later periods of castration they increased rapidly in percentage, while the level of the basophiles decreased. No marked changes were observed in the eosinophiles; however, they were decreased slightly in percentage.

3. Cryptorchism up to 180 days resulted in a mild increase in the basophilic elements (basophiles and castration cells). The level of the eosinophiles remained unchanged. The pituitary was not increased in weight.

4. Colloid was abundant in the residual clefts of the castrated rats.

5. A morphological comparison of the anterior pituitaries of male and female rats was presented.

**REFERENCES**

Addison, W. H. F.: J. Comp. Neurol. **28**: 441. 1917.
Cleveland, R. and J. M. Wolfe: Anat. Rec. **51**: 409. 1932.
Donaldson, H. H.: American Anat. Memoirs, No. 6. 1924.
Ellison, E. T. and J. M. Wolfe: Anat. Rec. **55**: 61. 1934.
Ellison, E. T. and J. M. Wolfe: Anat. Rec. **58**: 61. 1934.
Ellison, E. T. and J. M. Wolfe: Endocrinology **18**: 555. 1934.
Evans, H. M. and M. E. Simpson: Amer. J. Physiol. **89**: 371. 1929.
Martins, T. and A. Rocha: Mem. Inst. Oswaldo, Cruz, **25**: 73. 1931
Moore, C. R.: Am. J. Anat. **34**: 269. 1924.
Nelson, W. O.: Anat. Rec. **56**: 241. 1933.
Parks, M. E.: Anat. Rec. **58**: 83. 1934.
Schleidt, J.: Zentrabl. f. Physiol. **27**: 1170. 1913.
Severinghaus, A. E.: Anat. Rec. **57**: 149. 1933.
Stein, S. I.: Anat. Rec. **56**: 15. 1933.
Van Wagenen, Gertrude: Anat. Rec. **29**: 398. 1925.
Wolfe, J. M.: Proc. Soc. Exper. Biol. & Med. **32**: 186. 1934.
Wolfe, J. M. and E. T. Ellison: Anat. Rec. **58**: 93. 1934.
Zacherl: In Biedl's Innere Sekretion, **2**: 107. 1912.

# RESULTS OF PREOPERATIVE ADMINISTRATION OF AN EXTRACT OF PREGNANCY URINE: A STUDY OF THE OVARIES AND OF THE ENDOMETRIA IN HYPERPLASIA OF THE ENDOMETRIUM FOLLOWING SUCH ADMINISTRATIONS*

E. C. HAMBLEN, M.D.
*From the Department of Obstetrics and Gynecology*
*Duke University Hospital*
DURHAM, N. C.

A study of the ovaries and of the endometria obtained at operation from women who had received APL (anterior-pituitary lutenizing) extracts of pregnancy urine was begun three years ago. Preliminary reports (1) indicated that our findings corresponded closely to Engle's (2) observations following injections of an aqueous soluble pyridine extract in macacus monkeys but differed from the findings of Mandelstamm and Tschaikowsky (3) and of Geist (4).

Our preliminary reports were based on a series of 11 patients, while the present studies include material from 24 cases. In the series reported previously there were studies of 11 patients whose ages ranged from 13 to 44 years. Total doses of APL extract of pregnancy urine varied from 1200 R.U. to 8200 R.U. The menstrual histories and diagnostic studies permitted the following grouping: 6 with regular menstrual cycles; 3 with amenorrhea; 1 with hyperplasia of the endometrium; and 1 with inflammatory metrorrhagia. There were observed no hemorrhagic responses and no production of true corpora lutea but there was an apparent increase in the number of follicular cysts and in the degree of degenerative changes in maturing follicles. It was assumed at that time that the injections produced degeneration and atresia of the follicles and of the follicular cysts suppressing ovulation and subsequent corpus luteum formation. The recent studies have somewhat modified our impressions.

Mandelstamm and Tschaikowsky reported on the effects of daily subcutaneous injections of prolan varying from 100 to 200 M.U. with total doses from 400 to 1100 M.U. The 10 women studied had normal menstrual cycles and were operated upon on account of fibromyomata, carcinomata of the cervix or unilateral ovarian cysts. Six of the patients were between 30 and 40 years of age, two between 40 and 45 years and two between 20 and 30 years. The interval between the last injection and operation as well as the time in the menstrual cycle varied. They noted degenerative changes in the maturing and mature follicles which included defective ova and disintegrative and degenerative changes in the granulosa. There were cystic follicles, numerous corpora lutea and hemorrhages

*Read before the Eighteenth Annual Meeting of the Association for the Study of Internal Secretions, Cleveland, Ohio, June 11, 1934.

into the follicular apparatus. They felt that these changes were sufficient to produce a temporary sterility.

Geist has reported a study of the effect of injections of antuitrin-s on the mature human ovary from patients ranging in age from 33 to 48 years; the majority of those patients were operated upon because of uncomplicated fibroids. The total subcutaneous dosage varied from 600 to 2200 R.U.; total daily dosage was in some instances 600 R.U.; period of administration was from 36 to 100 hours. Geist noted occassional gross hemorrhages in the ovaries suggestive of a positive pregnancy test in the rodent. He was impressed also with the absence of what might be called follicle stimulation; the number of cystic follicles was increased apparently; theca lutein cells were thought to be increased. He thought that the intensity of the responses seen in the ovaries was directly proportional to the amount of injected hormone.

## CONDITIONS OF THE STUDIES

During the past three years we have collected material from 24 patients. We have been aided generously by the various members of our staff in the collection of operative specimens. We have excluded any patients in whom gross or clinical inflammatory processes or benign or malignant tumors of the generative system were present. Our attention has been confined to three general groups of patients: (1) those with known normal menstrual cycles; (2) those with hyperplasia of the endometrium; and (3) those with amenorrhea. In group I there were 9 patients who varied in age from 21 to 44 years; in group II, 11 patients whose ages varied from 16 to 43 years; and in group III, 4 patients whose ages varied from 13 to 38 years.

We have used a single commercial APL extract of pregnancy urine (antuitrin-s*). In the majority of instances it has been re-assayed in our laboratories for potency. The single, subcutaneous injection has varied from 100 to 400 R.U. The frequency of dosage has varied from one to four times daily. The total dosage has ranged from 800 to 8200 R.U. The duration of injections was three to 13 days. The time elapsing from the last injection to the laparotomy varied from one to 14 days. Injections were given on the second to the thirty-second day of the menstrual cycle. Laparotomy was performed on the eleventh to the fortieth day of the cycle.

At the time of laparotomy a careful gross study of both ovaries was recorded, including the size of the ovaries, presence and relative number of small cysts, presence or absence of recent or old corpora lutea, and any other significant findings. The amount of ovarian material available for microscopic study was as follows:

| | |
|---|---|
| Portion of one ovary | 4 cases |
| Portions of both ovaries | 2 cases |
| One entire ovary | 13 cases |
| Both ovaries | 4 cases |
| Portion of an ovary and an entire ovary | 1 case |

*Dr. E. A. Sharp of Parke, Davis & Company has furnished us generous amounts of antuitrin-s for these studies.

## TABLE I

### PATIENTS HAVING HYPERPLASIA OF THE ENDOMETRIUM

| Case Number | Age of Patient | Details of APL-P. U. Administration | | | | Time Elapsed Since Diagnosis by Curettage and Laparotomy/Days | Relative Number of Primordial Follicles Seen | Relative Number of Follicular Cysts Seen | Recent Corpora Lutea with Fresh Hemorrhage | Appearance of Endometrium After APL-P. U. Administration |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Average Single Dose/R.U. | Average Frequency | Number of Days Given | Total Dosage/R.U. | | | | | |
| X | 16 | 200 | 1x–4x | 6 | 3200 | Same | +++ | +++ | 0 | Interval glands, with variations in size and stroma of hyperplasia. |
| XI | 20 | 200–300 | 2x–4x | 9 | 8200 | 9 | +++ | ++++ | 0 | Interval glands, with moderate size irregularities. |
| XIII | 23 | 200–300 | 2x–4x | 7 | 7400 | 7 | ++++ | ++++ | 0 | Definite pattern of hyperplasia. |
| *XIV | 26 | 200 | 2x | 6 | 2400 | 8 | + | 1 | 0 | Interval glands with moderate size variations. |
| XII | 31 | 200 | 4x | 4 | 3200 | 7 | ++ | +++ | 0 | Interval glands with slight size variations. |
| XVI | 32 | 300 | 2x–3x | 4 | 3000 | 120 | ++ | + | + | Interval endometrium with moderate variations in size of glands. |
| XIX | 32 | 200–300 | 3x–4x | 7 | 6600 | 10 | ++ | + | + | Interval glands with moderate variations in size. |
| **III | 34 | 100 | 3x | 8 | 2400 | 4 | + | +++ | 0 | Five months after laparotomy: interval glands with moderate size variations. |
| XX | 40 | 200 | 1x–4x | 8 | 3000 | 13 | 0 | 2 | + | Premenstrual endometrium. |
| XVII | 42 | 200–400 | 1x–2x–3x | 5 | 4400 | 7 | + | + | + | Interval endometrium. |
| XVIII | 43 | 200–400 | 1x–2x–3x | 6 | 5400 | 11 | + | ++ | + | Interval glands with moderate variations in size. |

*Had had one-third skin erythema dose of deep x-ray to ovaries.
**Menses essentially normal, although curettage eight days before laparotomy showed polypoid hyperplasia; menorrhagia developed five months after laparotomy.

When only portions of ovaries were removed, the significant gross findings were included in these portions. Ovarian specimens upon removal were fixed promptly. In all instances sections were made at five micra in series, all ovarian tissue being available for study.

We shall confine our present study to a consideration primarily of the 11 patients with hyperplasia of the endometrium who have been classed in group II. In these patients, in addition to specimens of ovaries, we have secured a specimen of endometrium before administering the extract and another specimen following the conclusion of the series of injections. The time elapsing between the first diagnostic curettement and the specimen of endometrium following the series of injections has varied from four to 13 days, except in one instance where the interval was four months.

Figure I (Case 18) (X 6½)
Recent corpus luteum observed in Case 18 following APL extract administration.

MICROSCOPIC FINDINGS IN PATIENTS WITH HYPERPLASIA

I. *Ovaries*

(a) *Primordial and Early Follicles.* These are not affected in number or character. In case 14, in which only a very few primordial follicles were seen, only one developing follicle was observed in spite of a total administration of 2400 R.U. of the APL extract with single doses of 200 R.U. twice daily.

(b) *Maturing and Mature Follicles.* (1) Number—The findings of the microscopic studies of mature and maturing follicles are given in Table II.

| | |
|---|---|
| Many (ages 20 and 23) | 2 cases |
| Moderate number | 3 cases |
| Only two | 1 case |
| Only one | 3 cases |
| None | 2 cases |

(2) Degenerative Changes—All maturing or mature follicles studied have shown degenerative changes. Evidences of granulosal degeneration, primarily of cytolytic type, are observed generally (see Table II). Occasionally, in cases 3 and 10, suggestive granulosal luteinization was seen.

## TABLE II
### Study of Maturing and Mature Follicles

| Case Number | 10 | 11 | 13 | 14 | 12 | 16 | 19 | 3 | 20 | 17 | 18 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Age | 16 | 20 | 23 | 26 | 31 | 32 | 32 | 34 | 40 | 42 | 43 |
| Cytolytic Degeneration | ++(2) | +++ | +++ | +(1) | ++ | 0* | +(1) | ++ | 0* | +(1) | ++ |
| Theca Interna Proliferation | + | ++ | + | 0 | ++ | 0 | + | + | 0 | + | + |
| Granulosa Luteinization | + | 0 | 0 | 0 | 0 | 0 | 0 | + | 0 | 0 | 0 |
| Perifollicular Hemorrhage | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Intrafollicular Hemorrhage | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | + | ++ |
| Dosage APL Extract—Individual Dose/R. U. | 200 | 200–300 | 200–300 | 200 | 200 | 300 | 200–300 | 100 | 200 | 200–400 | 200–400 |
| Total Dosage/R. U. | 3200 | 8200 | 7400 | 2400 | 3200 | 3000 | 6600 | 2400 | 3000 | 4400 | 5400 |

*No maturing or mature follicles seen. (1), (2), etc.—Numerals refer to number seen.

## TABLE III
### Study of Follicle Cysts

| Case Number | 10 | 11 | 13 | 14 | 12 | 16 | 19 | 3 | 20 | 17 | 18 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Age | 16 | 20 | 23 | 26 | 31 | 32 | 32 | 34 | 40 | 42 | 43 |
| Cytolytic Degeneration | + | +++ | ++ | 0* | + | +(1) | ++ | +(1) | +(2) | ++ | + |
| Theca Interna Proliferation | +++ | ++ | ++++ | 0 | +++ | 0 | + | 0 | 0 | 0 | ++ |
| Granulosa Luteinization | + | 0 | ++ | 0 | +++ | 0 | 0 | 0 | 0 | + | ++ |
| Perifollicular Hemorrhage | 0 | 0 | 0 | 0 | + | 0 | + | 0 | 0 | 0 | 0 |
| Intrafollicular Hemorrhage | +(1) | 0 | +++(6) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Mitotic Figures seen in Granulosa | 0 | 0 | + | 0 | + | 0 | 0 | 0 | 0 | 0 | 0 |
| Ova in Cysts | 0 | +++(4) | +++(4) | 0 | +(1) | 0 | ++(2) | 0 | 0 | 0 | 0 |
| Dosage APL Extract—Individual Dose/R. U. | 200 | 200–300 | 200–300 | 200 | 200 | 300 | 200–300 | 100 | 200 | 200–400 | 200–400 |
| Total Dosage/R. U. | 3200 | 8200 | 7400 | 2400 | 3200 | 3000 | 6600 | 2400 | 3000 | 4400 | 5400 |

*No follicle cysts seen. (1), (2), etc.—Numerals refer to number seen.

(3) Hemorrhage—Perifollicular hemorrhage is not observed in relation to any of the maturing or mature follicles. Intrafollicular hemorrhage is observed in several instances in two cases (numbers 17 and 18). Both of these patients showed recent corpora lutea with an abundance of fresh hemorrhage; the follicles with hemorrhage were observed in the same ovary as the corpora lutea. Surgical trauma has been considered as a cause of much of this hemorrhage for it has been observed more commonly in cases in which only a portion of the ovary was removed.

(4) Changes in Stroma About Follicles—Definite proliferation of the theca interna in which the theca lutein cells were very conspicuous was observed in eight of the 11 cases. The three patients in whom this proliferation was absent showed no follicles in two instances and only one in the other.

(c) *Follicular Cysts.* (1) Number—The relative numbers of follicular cysts seen is shown in Table I. In general follicular cysts are encountered much more frequently in the younger age group of patients with hyperplasia than in the older age group. Four patients in the younger age group (ages 16, 20, 23, 31) showed the greatest number of cysts.

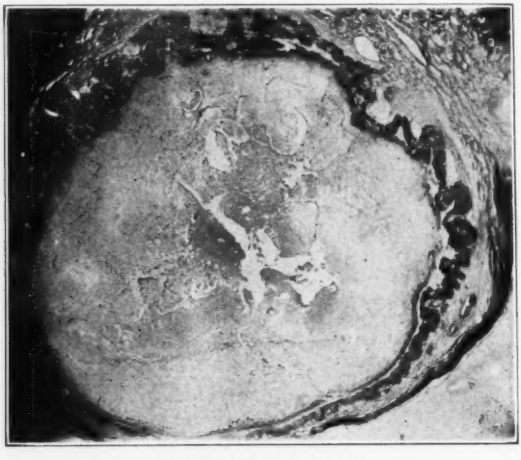


Figure II (Case 20) (X 5)
Recent corpus luteum observed in Case 20 following APL extract administration.

(2) Degenerative Changes—Table III shows the details of microscopic findings in the study of follicular cysts. Cytolytic degenerative changes in the granulosa were observed in varying degrees in all 10 of the patients in whom follicular cysts were seen. In five of these 10 patients there was observed apparent evidence of granulosal luteinization.

(3) Hemorrhage—Perifollicular hemorrhage in small amounts was observed in several instances in cases 12 and 19. Intrafollicular hemorrhage was observed in one cyst in patient 10 and in six cysts in patient 13. Neither of these patients showed corpora lutea.

(4) Ova—Ova in fair state of preservation were observed within follicular cysts in four patients: case 12, one ovum; case 19, two ova; cases 11 and 13, four ova. Mitotic figures were observed in the granulosa about the ova in cases 12 and 13.

(5) Changes in the Stroma About Follicular Cysts—Six of the subjects showed definite proliferation of the theca interna about the cyst walls, giving them in many instances the appearance of pseudo-lutein cysts; this was most marked in cases 10, 12 and 13.

(d) *Corpora Lutea and Corpora Albicantia.* Table IV summarizes the findings of the microscopic studies of corpora lutea and corpora albicantia. No recent corpora lutea occurred in the younger age group (ages 16, 20, 23, 26, 31, 34); they were observed, however, in the older age group (ages 32, 32, 40, 42,

## TABLE IV

### Study of Corpora Lutea and Corpora Albicantia

| Case Number | 10 | 11 | 13 | 14 | 12 | 16 | 19 | 3 | 20 | 17 | 18 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Age | 16 | 20 | 23 | 26 | 31 | 32 | 32 | 34 | 40 | 42 | 43 |
| Present | 0 | 0 | 0 | 0 | 0 | + | + | 0 | + | + | + |
| Recent Corpus Luteum— Day of Cycle | X | X | X | X | X | X | X | 33 | X | X | X |
| Increase of Size | X | X | X | X | X | 0 | ++ | X | +++ | + | ++ |
| Increase of Hemorrhage | X | X | X | X | X | + | ++ | X | ++ | ++ | ++ |
| Recency of Hemorrhage | X | X | X | X | X | ++++ | ++++ | X | ++ | +++ | +++ |
| Recency of Lutein Cells | X | X | X | X | X | ++++ | ++++ | X | ++ | +++ | +++ |
| *Other CL or CA showing recent H or PL | CA 1 H | 0 | CA 1 H | 0 | 0 | 0 | 0 | 0 | CA 1 H | CL 1 PL H | 0 |
| Dosage APL Extract— Individual Dose/R. U | 200 | 200–300 | 200–300 | 200 | 200 | 300 | 200–300 | 100 | 200 | 200–400 | 200–400 |
| Total Dosage/R. U | 3200 | 8200 | 7400 | 2400 | 3200 | 3000 | 6600 | 2400 | 3000 | 4400 | 5400 |

*CL—Corpus luteum. CA—Corpus albicans. H—Persisting hemorrhage. PL—Persisting lutein cells.

43). The corpora in four of these five patients were thought to be moderately larger than normal and in all five patients there seemed to be more abundant hemorrhage than was seen in patients with normal menstrual cycles who had received APL extract previous to or during the time of ovulation. The recentness of the hemorrhage and of the lutein cells were well within agreement. In cases 10, 13 and 20 old corpora albicantia with recent remorrhage were observed. Patient 17 showed an old corpus luteum with recent hemorrhage and persisting lutein cells.

Figure III (Case 13) (X 120)
Walls of two follicular cysts seen in Case 13.

Figure IV (Case 13) (X 120)
Proliferation of theca interna with characteristic theca lutein cells and dilated vessels in the theca interna is observed.

II. *Endometrium*

Table I gives the character of endometrium observed after APL extract administration. In only one instance (where the time elapsed between the first curettement and the hysterectomy was 13 days) was premenstrual endometrium observed; a recent corpus luteum was observed in the ovary at laparotomy in this case. The endometria following medication in the other 10 cases showed interval glands with or without moderate size variations.

DISCUSSION

It seems evident from our studies of the patients with hyperplasia of the endometrium as well as of those with normal menstrual cycles and of those with amenorrhea that primordial and early follicles are not affected in number or character by APL extract injections.

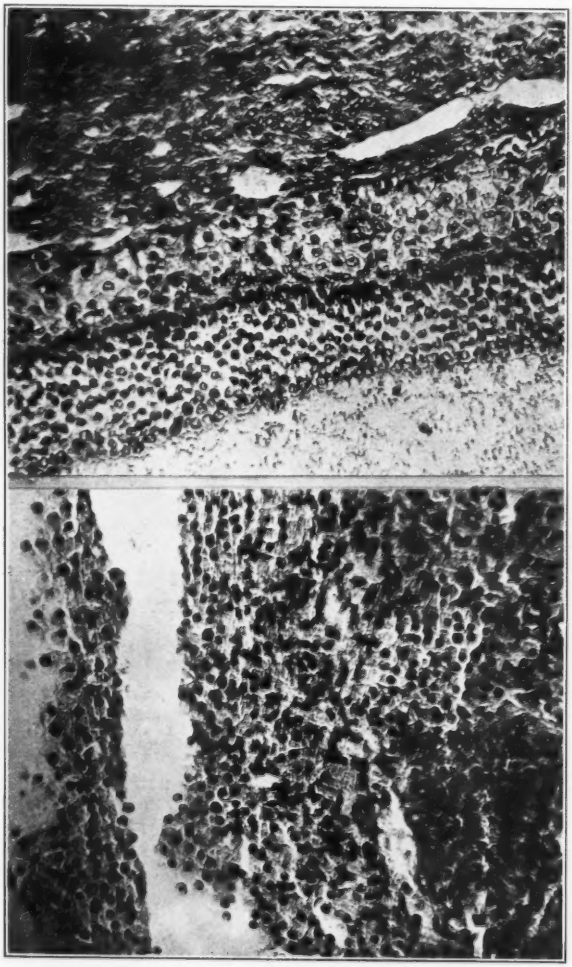


Fig. V

Fig. VI

Figure V. (Case 12.) (X 200.) Wall of follicular cyst showing apparent granulosa luteinization.
Figure VI. (Case 18.) (X 200.) Wall of follicular cyst showing proliferation of theca interna and apparent granulosa luteinization.

The degenerative changes in maturing and mature follicles as well as the presence of degenerating follicular cysts are to be expected in the life cycle of graafian follicles. Engle notes, "Save for the granulosa cells which undergo lysis in atretic follicles, there is no other fate for granulosa cells than that of transformation into lutein tissue." Our present concepts of the etiology of hyperplasia of the endometrium lead us to expect evi-

dence of increased degenerative processes. In this series of patients we feel that these changes are increased as compared with the other two groups of patients studied (those with normal menstrual cycles and those with amenorrhea). The younger age group of patients in this series shows these changes more frequently than the older age group. This is to be expected from the higher index of follicular activity in the younger patients. Sharp's (5) theory of relative immaturity in these patients suggested to me by him and as quoted by Pratt (6) may explain differences in responses of the two age groups. Proliferation of the theca interna with very conspicuous theca lutein cells suggests true luteinization in many instances; this is most marked in the younger age group. Clinical experi-

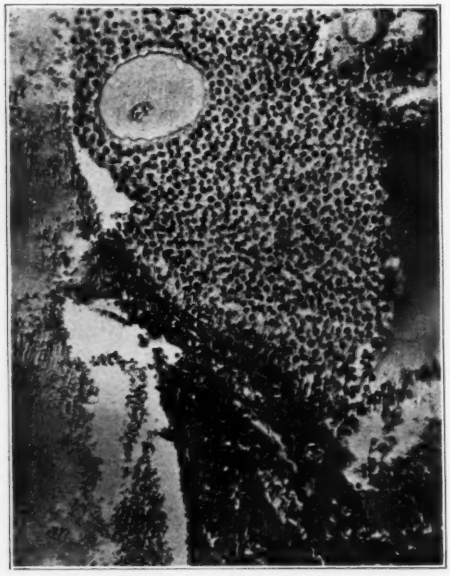


Figure VII. (Case 13.) (X 120.) Mature follicle showing degenerating ovum and granulosa. There is fresh hemorrhage into the follicle and suggestive luteinization of the follicle wall.

ences do not allow any inferences to be drawn as to function similar to that attributed to true lutein tissue. The presence of mitotic figures in the granulosa about ova in certain follicular cysts would suggest either the recent formation of the cyst or reactivation of the cyst wall. One is privileged, perhaps, from these findings to conclude that APL extract probably acts primarily upon the developing and maturing follicles producing degenerative changes, especially those of cystic degeneration and of proliferation of the theca interna.

Hemorrhagic changes, either about follicles and follicular cysts or into follicles and cysts, have not formed a consistent or striking part of

our observation, occurring in approximately one-half of the instances in association with recent corpora lutea.

Our previous studies had led us to assume that ovulation was not produced by APL extract injections. Its occurrence was not observed in patients with amenorrhea nor in the younger age group of patients with hyperplasia. Where recent corpora lutea were observed in patients with normal menstrual cycles, they conformed to the time of the menstrual cycle. The consistent occurrence of recent corpora lutea in patients of the older age group with hyperplasia requires the conclusion that ovulation resulted from the APL extract injections if we accept the present concepts of the etiology of hyperplasia as emphasized by Burch and his co-workers (7). It is to be noted that in general the younger age group of patients, whose ovaries showed characteristically plentiful primordial follicles and follicular cysts, did not show recent corpora lutea, while those patients in the older age group, whose ovaries showed infrequent priordial follicles and follicular cysts, showed recent corpora lutea. Maturity and immaturity factors probably explain this difference in response.

Witherspoon's (8) conception of prolonged hyperplasia as a cause of fibromyomatous changes may allow an explanation of the disagreements between the reports of Geist and Mandelstamm and Tschaikowsky and our observations, as the majority of the patients in these two studies was in the older age group and the indication for operation was almost uniformly fibromyomata.

As to the minimal effective dose of APL extract there is little we are warranted in concluding. Injections of 200 R.U. of APL extract, one to two times daily, for a period of eight days, and with a total dosage of 3000 R.U., resulted in a corpus luteum in the ovary of a patient of the older age group with hyperplasia. On the other hand, injections of 200 to 300 R.U., two to four times daily, over a period of nine days and with a total dosage of 8200 R.U., failed to produce a corpus luteum in a girl of 20 with hyperplasia.

The results of endometrial studies are not worthy of much discussion. It seems reasonable that if a longer interval had elapsed after the initial injection of APL extract, premenstrual endometria would have been observed in all of the five patients in whom recent corpora lutea were seen; and, vice versa, no premenstrual changes would have been expected in those six patients in which no recent corpora lutea were seen.

## SUMMARY AND CONCLUSIONS

1. A study of the ovaries and of the endometria of 11 patients with hyperplasia of the endometrium following injections of an APL extract is presented. Single injections ranged from 100 to 400 R.U.; frequency of administration varied from one to four times daily. The duration of injections varied from four to nine days and the total dosage from 2400 to 8200 R.U. Patients with gross inflammatory changes or with benign or malignant tumors of the generative tract were not studied. Endometrial

specimens were obtained before administration of the extract and after the injections of extract at the same time as the ovarian specimens.

2. It seems evident that APL extract does not affect primordial or early follicles and that it acts primarily upon maturing and mature ones, increasing the degenerative changes commonly observed and probably producing cystic degeneration.

3. The response in the younger age group (immaturity) is different from that of the older age group (maturity) of patients with hyperplasia.

4. Recent corpora lutea are produced apparently in the latter group by injections of APL extract.

5. Hemorrhage into or about follicles constitutes an unimportant finding.

6. Endometrial changes were produced in but, perhaps, a single instance.

We wish to express our appreciation to Dr. J. P. Pratt for his help in these studies and for many helpful suggestions. We are indebted also to members of our staff for help in the collection of operative specimens. Dr. Wiley D. Forbus of the Department of Pathology has aided us materially by supplying assistants for a large part of the technical work.

## REFERENCES

1. Hamblen, E. C.: The present status of the female sex hormones in the treatment of disorders of menstruation. South. Med. & Surg. **34,** 339. 1932; Pan-American Medical Assn., Dallas, Texas, March 21-25. 1933; Reference by J. P. Pratt, Sex and Internal Secretions, Pp. 900-901, Williams & Wilkins, Baltimore, 1932; Human ovarian responses to extracts of pregnancy urine—Preliminary Report, Virginia Med. Monthly, **60:** 286. 1933.
2. Engle, E. T.: Effects of extracts of the anterior pituitary and similar active principles of blood and urine, Sex and Internal Secretions, Pp. 794; 796-797; Williams and Wilkins Co., Baltimore, 1932.
3. Mandelstamm, A. and W. K. Tschaikowsky: Zur hormonalen Sterilisierung des Weibes. (Untersuchungen über die Wirkung des Prolans auf die Eierstöcke), Arch. f. Gynäk. **151:** 686. 1932.

———————: "Hormone sterilization of female organism," Vrach. delo. Nos. **17-20:** 99. 1932; Abst., J. A. M. A. **100:** 1763. 1933.

4. Geist, S. H.: Reaction of the mature human ovary to Antuitrin-S, Am. J. Obst. & Gynec. **26:** 588. 1933.
5. Sharp, E. A.: Personal communication.
6. Pratt, J. P.: Endocrine disorders in sex function in man, Sex and Internal Secretions, P. 901, Williams & Wilkins Co., Baltimore. 1932.
7. Burch, J. C., W. L. Williams and R. S. Cunningham: The etiology of endometrial hyperplasia, Surg. Gynec. and Obst. **53:** 338. 1931.
8. Witherspoon, J. T.: A possible cause of uterine fibroids, Endocrinology, **17:** 703. 1933.

# HORMONIC SYMPTOMATOLOGY OF THE THYROID: TO WHAT EXTENT IS IT EXPLICABLE ON THE BASIS OF ALTERED METABOLIC RATE*

J. H. MEANS AND J. LERMAN
*From the Thyroid Clinic of the Massachusetts General Hospital*
BOSTON

Compared with that of some other endocrine glands, the hormonic symptomatology of the thyroid should be easy to interpret. So far as known, the thyroid has the sole function of manufacturing the hormone thyroxin. The biologic rôle of this substance has, to a considerable extent, been identified. It is desirable, therefore, to attempt to translate clinical phenomena into terms of known physiological actions. Although in the case of thyroxin, as with other hormones, these actions are doubtless several, we have become accustomed in clinical work to think largely in terms of its calorigenic action. This is because we make use of calorigenic action, in the form of basal metabolic rate, to measure the degree of hyperthyroidism or hypothyroidism in our patients.

The recent appearance on the medical scene of such new calorigenic substances as dinitrophenol and dinitro-ortho-cresol (1, 2, 3) makes far easier than heretofore the separation of the hormonic symptomatology of the thyroid into a panel explicable on simple changes in heat production, and a panel which must be attributed to actions of thyroxin other than calorigenic.

If one gives to persons free from thyroid disease sufficient thyroid or thyroxin to elevate the basal metabolic rate, let us say, to plus 20, or thereabouts, there will develop a variety of symptoms. These will undoubtedly include tachycardia, palpitation, feeling of warmth, increased sweating, irritability, restlessness and trembling. There may also be precordial pain, insomnia, diarrhoea and asthenia. Such symptoms are not infrequently seen in women who attempt weight-reduction by self-dosing with thyroid.

It has been found of late by several observers that even if much higher elevations in metabolism are induced by the administration of dinitrophenol or dinitro-ortho-cresol, but few of these symptoms appear. Furthermore, the English investigators, Dodd and Robertson (4) have made the interesting observation that the metabolic rate of a myxedema patient can be maintained at a level between plus 20 and plus 30 for over a week, by means of dinitro-ortho-cresol, without the slightest change in the myxedema symptom-picture.

At the Massachusetts General Hospital four patients suffering from arthritis have had their metabolic rates raised by means of dinitrophenol

*Read before the Eighteenth Annual Meeting of the Association for the Study of Internal Secretions, Cleveland, Ohio, June 12, 1934.

by Dr. W. Bauer, et al., and we have observed them carefully and questioned them about symptoms. Not one of them would admit of any symptom whatever beyond slight feeling of warmth and slight increase in sweating, and in one case appetite improvement, although the basal metabolic rates reached were at times plus 60 and above. In these cases the hypermetabolism was not maintained longer than five days at a time, but cases reported in the literature have been kept at an elevated level for weeks without developing symptoms suggestive of thyrotoxicosis.

It is evident, therefore, that although thyroxin and dinitrophenol are alike in exerting a calorigenic action, they differ widely in other respects, thyroxin producing many phenomena which dinitrophenol does not.

One of the most remarkable facts about the action of dinitrophenol is that pulse elevation either occurs not at all, or is far less than one would expect for the metabolic rate increase were the latter due to any other known calorigenic agent or agency. Some years ago Minot and Means (5) showed that in both thyrotoxicosis and leukemia there is an approximately linear relationship between basal metabolic rate and pulse, and that it is essentially the same in the two diseases. Also it has been shown by various observers that in the performance of muscular work (6, 7) an essentially linear relationship exists between pulse rate and metabolic rate. Furthermore, studies of the minute volume of the heart in muscular work and in thyrotoxicosis (8) show that this function and metabolic rate accelerate in more or less parallel fashion. In the case of adrenalin, certain observations made in this clinic (8) some years ago indicate that not only do pulse rate and cardiac output increase coincidentally with metabolic rate, but in more than equal proportion. While a 65 per cent increase in oxygen demand caused by thyrotoxicosis called forth an 86 per cent increase in cardiac output, a 20 per cent increase in metabolic rate due to adrenalin called forth a 94 per cent increase in cardiac output. Adrenalin seems, therefore, to whip up heart output in greater degree than metabolism.

All of these facts which might be interpreted to signify that whenever the call for oxygen by the tissues is increased there will be increased circulatory activity, make the hemodynamics of dinitrophenol very puzzling. What happens when a 60 per cent metabolic rate increase is accompanied by little or no pulse increase? To throw light on this problem, complete hemodynamic studies were made, at our request, in three of Bauer's patients. The results are shown in Table I.

What hits one in the eye here is that marked increase in metabolism calls forth little or no rise in pulse. The method of getting the extra oxygen in, however, differs among the three subjects. In the case of P., recourse is had to greater reduction of hemoglobin as blood passes capillaries, with no alteration in cardiac output. In the case of J., reduction of hemoglobin is no greater after the drug than before, but cardiac output is increased. T. apparently makes some use of both expedients. This is what the California investigators (9) found in animals. Thus the hemo-

TABLE I

EFFECT OF DINITROPHENOL IN THREE ARTHRITIC PATIENTS
HEMODYNAMICAL DATA

| Patient | P. | | T. | | J. | |
|---|---|---|---|---|---|---|
| | Before | After | Before | After | Before | After |
| Basal metabolic rate | Normal | +70 | −14 | +68 | −16 | +54 |
| Pulse | 62 | 64 | 70 | 84 | 60 | 66 |
| Cardiac output (liters per minute: Grollman method) | 4.6 | 4.74 | 3.4 | **5.2** | 3.5 | **4.2** |
| Arterial oxygen saturation, volume per cent | 95 | 95 | 97.2 | 95.8 | 96.0 | 96.0 |
| Venous oxygen saturation, volume per cent | 79 | **46** | 67.2 | **62.1** | 45.0 | 45.0 |
| Velocity (arm-tongue time: seconds) | 21.0 | 13.2 | 13.6 | 9.4 | 12.8 | 12.0 |

Note: Peripheral dilation, as evidenced by a significant rise in skin temperature after administration of the drug, was noted in all three cases.

dynamical response to the calorigenic action of this drug is quite different from that to the physiologic calorigenic agents, namely, work, adrenalin and thyroxin. The velocity of blood flow, which was determined in these three patients by the injection of "Decholin" into the arm vein and noting the time required for the taste reaction is difficult to interpret. In patients T. and J., velocity paralleled cardiac output, but in patient P., velocity increased while cardiac output did not. If we seek an explanation in the peripheral circulation, we become further confused, because in each case there was evidence of dilatation. A constant rate of cardiac output with widened peripheral vascular bed should give a slower velocity. Of course, total vascular bed may not be increased in any of these cases. Deep constriction may more than offset superficial dilatation.

Let us now pass for a moment to the territory of hypometabolism. We have recently shown (10), by the analysis of fifty cases of spontaneous myxedema, that myxedema symptoms are closely related to metabolic rate, being usually absent until the basal metabolic rate has sunk to minus 20 and only full-blown when it has sunk below minus 30. The same experience has been had by Blumgart, et al. (11) in artificial myxedema. Nevertheless, we have seen on the one hand that in Dodds and Robertson's case the picture of myxedema was present with a metabolic rate in the plus 20s, for a week, when dinitrocresol was given, and, on the other hand, we have ourselves seen a number of patients with levels of metabolism at times definitely below minus 30 without the picture of clinical myxedema. These were all patients with no evidence of thyroid disease. Their hypometabolism was not, we believe, of thyroid origin. Their diagnoses were as follows:

One was a boy of fourteen with narcolepsy; another a man of twenty-five with certain hysterical manifestations. Five were adolescent girls with malnutrition. One was a tired, neurotic business man of forty-eight, a private patient of Dr. M. Fremont-Smith, to whom we are indebted for

the observation. On several occasions, over a two-year period, his basal metabolic rate had been below minus 30 and on the day he was seen by one of us it was minus 48; yet he presented no clinical suggestion of myxedema whatever. Two patients with gout, who have been in our Metabolism Ward for long periods, have repeatedly shown rates below minus 30 and no suggestion of myxedema. One patient with idiopathic hypochromic anemia showed a steadily falling metabolism, down to minus 35, without clinical myxedema. One remarkable patient, showing extreme somnolence but no other symptoms or signs suggesting myxedema, had on different days, rates of minus 36, minus 43, minus 38 and minus 46. She turned out to have a suprasellar cyst, which was evacuated, after which her somnolence disappeared and she felt well. Her basal metabolic rate rose to minus 27 without any thyroid medication.

TABLE II

HORMONIC SYMPTOMATOLOGY OF THE THYROID

| Type of Hormone Action | In Thyrotoxicosis | In Myxedema |
|---|---|---|
| I. Calorigenic. | Sensation of warmth.<br>Increased sweating.<br>Warm, moist skin.<br>Peripheral dilatation.<br>Weight loss. | Chilliness.<br>Decreased sweating.<br>Dry, cold skin.<br>Weight gain (in part). |
| II. Hemodynamic. | Tachycardia.<br>High pulse pressure.<br>Increased cardiac irritability.<br>Increased cardiac output.<br>Precordial pain. | Bradycardia.<br>Low pulse pressure.<br>Lowered cardiac tonus.<br>Decreased cardiac output. |
| III. Neurotropic. | Increased irritability.<br>Overactivity.<br>Active cerebration.<br>Intoxication—Psychosis.<br>Tremor.<br>Palpitation (?).<br>Diarrhoea. | Complacency.<br>Underactivity.<br>Slow cerebration.<br>Sleepiness.<br>Loss of memory.<br>Diminished sensory acuity (sight, hearing, other ?).<br>Constipation. |
| IV. On the distribution and composition of body fluids. | | Edema, pitting and non-pitting.<br>Edema of heart muscle.<br>Macroglossia (?).<br>Hyperproteinemia.<br>Decreased blood volume (15).<br>Increased deposit protein (16).<br>Increased spinal fluid protein (17).<br>Weight gain (in part).<br>Albuminuria. |
| V. On tissue growth and Differentiation. | Rapid growth of thyrotoxic children (?). | Coarse skin.<br>Coarse, brittle hair.<br>Slow skin, hair and nail growth.<br>Anemia (?).<br>Dwarfism of the cretin.<br>Immaturity of the cretin.<br>Imbecility of the cretin. |
| VI. On other endocrines. | Increased sexual activity.<br>Oligomenorrhoea—Amenorrhoea.<br>Increased sensitivity to adrenalin. | Decreased sexual activity.<br>Menorrhagia.<br>Sterility.<br>Failure to develop sex characters in the cretin and juvenile myxedema<br>Decreased sensitivity to adrenalin. |
| VII. Unclassifiable. | Increased appetite.<br>Eye signs.<br>Myasthenia and muscular atrophy.<br>Increased tolerance to certain drugs: Morphine.<br>Low sugar tolerance.<br>Hypocholesterolemia (?).<br>Increased excretion of calcium and phosphorus (18).<br>Creatinuria. | Decreased appetite.<br>Hoarseness.<br>Decreased tolerance to certain drugs: Morphine, digitalis (?).<br>High sugar tolerance.<br>Hypercholesterolemia.<br>Decreased excretion of calcium and phosphorus (18). |

Other cases might be mentioned, but this list will suffice to indicate the variety of cases in which hypometabolism, probably not of thyroid origin, is encountered. The only symptoms these people showed which may have been due to low basal metabolic rate were chilliness, decreased sweating and sometimes coarse skin. The work of Hurxthal, et al. (12) is of interest in this connection. These investigators showed that in true hypothyroidism blood cholesterol is elevated (usually over 250 milligrams per 100 cc. of blood), while in persons with low rate and no picture of myxedema, blood cholesterol values are within normal limits.

Thus it is evident that just as the picture of thyrotoxicosis is not entirely explicable on the basis of hypermetabolism, neither is that of myxedema explicable alone on that of hypometabolism. Both these pictures are specific to the thyroid and constitute uniquely hyperthyroidism and hypothyroidism. These terms are in no sense synonymous with hypermetabolism and hypometabolism, as some writers would have us believe: nor are dinitrophenol and dinitrocresol in any sense substitutes for thyroid in the treatment of genuine hypothyroidism. This should be stressed for one finds in the literature conflicting statements. For example, we find Cutting, Mehrtens and Tainter (13) saying in one place: "Doses within therapeutic range cause in man significant increase in metabolism without fever, which may be useful in the treatment of obesity, hypothyroidism and similar depressed metabolic states," while in another report, Cutting and Tainter (14), speaking of the failure of dinitrophenol to accelerate metamorphosis in amphibians, say: "Accordingly dinitrophenol lacks the hormonal actions of thyroid and should probably not be used therapeutically to replace the gland in true thyroid deficiencies." Our own view agrees with the latter, not the former statement.

## SUMMARY

On the basis of comparisons of the symptoms and signs of hyperthyroidism with those of hypermetabolism, produced by calorigenic agents other than thyroxin on the one hand and of the symptoms and signs of hypothyroidism with those of hypometabolism in persons without discoverable thyroid disease on the other, the attempt has been made to divide thyroid hormonic symptomatology in a calorigenic and a non-calorigenic panel. The results of this attempt are given in Table II. This exposition, it should be understood, is both incomplete and tentative. It is in no sense an exact analysis of the hormonology of thyroxin, but an interpretation of clinical symptoms and signs and laboratory findings which it is hoped may be helpful in the understanding of thyroid disease.

The study indicates that the symptoms attributable simply to increased heat production consist in not much more than increased sweating, sensation of warmth, warm skin, flushing and weight loss, and those of simple decreased heat production consist in decreased sweating, chilliness, dry, cold skin and to some extent weight gain.

The other symptoms and signs of hyperthyroidism and hypothyroidism are due to physiologic actions of thyroxin other than its calorigenic and the whole picture in these conditions is specific to the thyroid and not a simple matter of metabolic rate alteration.

**REFERENCES**


1. Magne, H., A. Mayer and L. Plantefol: Action pharmacodynamique des phénols nitrés: Un agent augmentant les oxydations cellulaites, Ann. de Physiol. **8:** 1; 51; 70; 157. 1932.
2. Cutting, W. C. and M. L. Tainter: Actions of dinitrophenol, Proc. Soc. Exper. Biol. & Med. **29:** 1268. 1932.
3. Dodds, E. C. and W. J. Pope: Dinitro-o-cresole as a stimulator of metabolism, Lancet, **2:** 352. 1933.
4. Dodds, E. C. and J. D. Robertson: The clinical application of dinitro-o-cresol, Lancet, **2:** 1197. 1933.
5. Minot, G. R. and J. H. Means: The metabolism-pulse ratio in exophthalmic goiter and in leukemia, Arch. Int. Med. **33:** 576. 1924.
6. Boothby, W. M.: A determination of the circulation rate in man at rest and at work. Am. J. Physiol. **37:** 383. 1915.
7. Means, J. H. and L. H. Newburgh: The effect of caffeine upon the blood flow in normal human subjects. J. Pharmacol. & Exper. Therap. **7:** 449. 1915.
8. Means, J. H.: Circulatory disturbances in diseases of the glands of internal secretion. Endocrinology. **9:** 192. 1925.
9. Hall, V. E., J. Field, 2nd., M. Sahyun, W. C. Cutting and M. L. Tainter: Carbohydrate metabolism, respiration and circulation in animals with basal metabolism heightened by dinitrophenol. Am. J. Physiol. **106:** 432. 1933.
10. Means, J. H. and J. Lerman: The symptomatology of myxedema: Its relation to metabolic levels, time intervals and rations of thyroid, Tr. A. Am. Physicians, **49:** 214. 1934.
11. Gilligan, D. R., M. C. Volk, D. Davis and H. L. Blumgart: The relationship between serum cholesterol, basal metabolic rate and the clinical aspects of hypothyroidism. Arch. Int. Med. (In press.)
12. Mason, R. L., H. M. Hunt and L. Hurxthal: Blood cholesterol values in hyperthyroidism and hypothyroidism: Their significance. New England J. Med. **203:** 1273. 1930.
13. Cutting, W. C., H. G. Mehrtens and M. L. Tainter: Actions and uses of dinitrophenol, promising metabolic applications. J. A. M. A. **101:** 193. 1933.
14. Cutting, C. C. and M. L. Tainter: Comparative effects of dinitrophenol and thyroxin on tadpole metamorphosis. Pro. Soc. Exper. Biol. & Med. **31:** 97. 1933.
15. Thompson, W. O.: The blood volume in myxedema with a comparison of plasma volume changes in myxedema and cardiac edema. J. Clin. Invest. **2:** 477. 1926.
16. Boothby, W. M., I. Sandiford, K. Sandiford and J. Slosse: Effect of Thyroxin on the Respiratory and Nitrogenous Metabolism of Normal and Myxedematous Subjects. Tr. A. Am. Phys. **40:** 195. 1925.
17. Thompson, W. O., P. K. Thompson, E. Silveus and M. E. Dailey: Protein Content of the Cerebrospinal Fluid in Myxedema. J. Clin. Investigation, **6:** 251. 1928.
18. Aub, J. C., W. Bauer, C. Heath and M. Ropes: Studies of calcium and phosphorus metabolism: III. The effects of the thyroid hormones and thyroid disease. J. Clin. Investigation, **7:** 97. 1929.

# CONCERNING THE ANTERIOR PITUITARY-GONADAL INTER-RELATIONS*

WARREN O. NELSON
*Department of Anatomy, University of Missouri*
COLUMBIA, MO.

With recent progress in the field of endocrine physiology we are recognizing the existence of an extensive inter-relationship among the various endocrine glands and their hormonal products. In some instances these relations appear to be of a reciprocal nature, i.e., each of a pair of inter-related glands exerts a controlling influence on the other member of the pair. The relation between the anterior hypophysis and the gonads would appear to be of this nature, and, furthermore, evidence is at hand which indicates that this relationship is active in the control of certain other physiological activities. In this paper it is proposed, in addition to outlining the general theory, to present physiological and histological evidence of the action of the gonad hormones on the anterior hypophysis and to consider the control of certain other physiological activities.

Although the earlier studies† of many others indicated the existence of a reciprocal influence between the anterior hypophysis and the gonads, Moore and Price (1) have presented the most complete and convincing evidence and the most adequate exposition of the subject. It has been shown that the gonads are dependent upon the anterior lobe hormone or hormones for their normal gametogenic and endocrine activities. In turn the gonad hormones exert a controlling influence upon the anterior lobe. Excessive or unusual endocrine activity of the gonads may be induced by administration of the hypophyseal gonad-stimulating hormone. On the other hand, the gonad hormones inhibit the secretion of the gonad-stimulating hormone. Removal of the gonads results in a release of the inhibiting factor and an abnormal activity of the anterior lobe. The administration of excessive amounts of gonad hormone results in diminished hypophyseal activity. This reciprocity of hormonal action results in a balanced control of the hypophysis and the gonads in the normal animal and almost certainly is an important factor in the regulation of sexual cycles.

Recognition should be given, at this time, to the fact that of all the recognized gonad hormones, both male and female, only the oestrogenic hormone has been definitely proven to have an inhibiting influence on the anterior hypophysis. Attention will be given, presently, to this question and its possible significance.

---

*Read before the Eighteenth Anuual Meeting of the Association for the Study of Internal Secretions, Cleveland, June 12, 1934.

†For a discussion of these studies the reader is referred to the paper by Moore and Price (1).

THE INFLUENCE OF THE GONADS UPON ANTERIOR LOBE HISTOLOGY

The hypothesis advanced by Kraus (2) that the chromophobe cells of the anterior lobe are the precursors of the two recognized chromophilic cell types, and that these cells, i.e., the acidophiles and basophiles, are independently functional units recently has received considerable support (3, 4, 5). This evidence from embryological and cytological sources has demonstrated that the chromophobes give rise independently to acidophiles and basophiles. Having assumed a granular form these cells each go through their own typical secretory cycle, pass through a stage of degranulation, and finally revert back to a chromophobic condition from which point the cycle may be repeated.

Excellent evidence has been advanced which indicates that in the rat and mouse, at least, the basophiles are concerned with the production of the gonadotropic principle† and the eosinophiles with the growth-promoting factor (6, 7, 8). The same relation is believed to hold for man (9). The recent report of Biggart (10) on the human pituitary after castration lends further support to this concept.

That there is a definite relation between the gonads, the basophiles, and the gonadotropic principle has been shown by the concurrence of an increase in gonad-stimulating substance and of profound changes in the basophiles following gonadectomy.

These castration changes are particularly well delineated in the rat hypophysis where, following gonadectomy, the basophiles rapidly increase in number and size (Fig. 1). During the second month after castration they begin to vacuolate. This vacuolation of the basophiles gives rise to the so-called "castration cells" (Fig. 3). A decrease in the number of acidophiles also occurs, but it is far less striking than the profound changes in the basophiles. The physiological and cytological changes induced by gonadectomy may be prevented or corrected by administration of gonad hormone (Figs. 1-4). Hohlweg and Dohrn (11) have shown that the injection of oestrin in gonadectomized mice prevents the pituitary castration changes in either sex, but that the male requires about six times as much oestrin as does the female for the production of equivalent effects. Nelson (12) has shown that a similar ratio holds for the effect of oestrin on the hypophyses of gonadectomized rats and, furthermore, that testis-hormone preparations also are effective in the same ratio, i.e., about five times as much hormone is required to prevent castration changes in the male as in the female. In experiments upon the guinea pig the writer has found that about three or four times as much oestrin is required to suppress lactation in properly prepared males as in females. It would appear that this sex difference in the oestrin threshold for suppression of the anterior pituitary

†The writer is intentionally avoiding a discussion of the two gonad-stimulating factors, follicle-stimulating and luteinizing, which have been recognized by some workers. Although very good evidence for the existence of two principles has been presented, there is, to the writer's knowledge, none which would show that the two principles are related to different anterior lobe cells. For this reason reference will constantly be made simply to the gonad-stimulating or the gonadotropic hormone.

is due to a definite genetical difference between the gland in the two sexes. Smelser (13) has presented evidence on this point which has been confirmed by the writer who spayed ten immature female guinea pigs. In each instance one ovary was grafted within the donor and the other ovary transplanted to a litter-mate brother. In the six pairs where both grafts

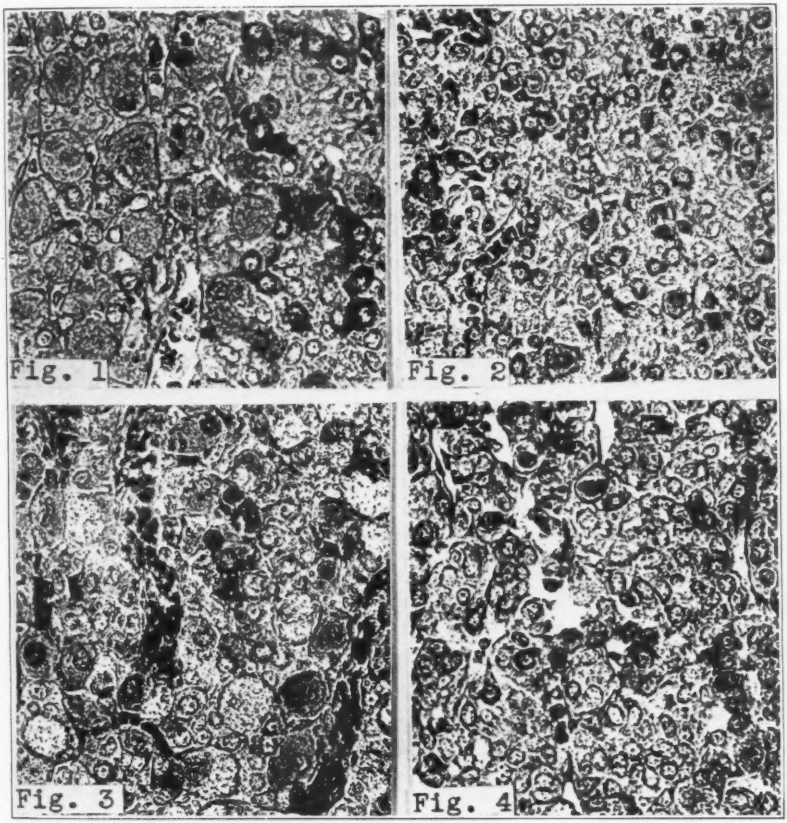



Figure 1. Anterior hypophysis from male rat H535. Castrated 30 days. No treatment Note many enlarged basophiles. x 435.

Figure 2. Anterior hypophysis from male rat H572. Castrated 30 days. Received 6 R.U. theelin in oil daily. Note essentially normal picture. x 435.

Figure 3. Anterior hypophysis from male rat H478. Castrated 200 days. No treatment. Note enlarged basophiles and signet-ring castration cells. x 360.

Figure 4. Anterior hypophysis from male rat H493. Castrated 230 days. Received 40 R.U. theelin in oil daily during last 30 days. Note essentially normal picture. x 360.

became functional the mammary gland development of the brother far exceeded that attained by the sister. Since development of the mammary gland depends upon oestrin and since all other factors were held constant in the experiment, this has been interpreted as evidence that the hypophysis of the male has an inherently greater gonad-stimulating capacity than

that of the female. Furthermore, Engle's (7) demonstration that in the rat the male hypophysis is more potent than the female in gonadotropic hormone has been confirmed repeatedly.

A comparison of the distribution of the anterior lobe cell types in male and female hypophyses has shown that the male gland has a higher percentage of basophiles, a lower percentage of eosinophiles and a higher percentage of chromophobes. This has been shown by Rasmussen (14, 15) for the human pituitary.

Employing the method of Rasmussen (16) the writer has made cell counts of the hypophyses from 68 normal male and 56 normal female rats. Several different technical methods have been employed in these studies, including the Champy fixation—Aultmann staining method outlined by Severinghaus (17), and Regaud, Zenker-formol, and Zenker-formol acetic fixations followed by different modifications of Mallory's triple stain. The averages for the male pituitary showed 8.1 per cent basophiles, 49.8 per cent acidophiles, and 42.1 per cent chromophobes. In the female hypophysis the basophiles averaged 4.2 per cent, the acidophiles 34.4 per cent, and the chromophobes 61.4 per cent. The larger number of basophiles in the male gland coincides with its greater potency in gonadotropic hormone and is further evidence that the basophiles are related to that hormone. Furthermore, in the light of the above findings, more than a casual significance must be attached to the demonstration that larger amounts of gonad hormone are required for the prevention of the changes in the basophiles of the male hypophysis following castration.

Therefore, it is apparent that certain basic facts stand out as presenting a working hypothesis for the understanding of the manner in which the gonad hormones effect a control over the basophilic elements of the hypophysis in the two sexes. Furthermore, on the basis of this interpretation the cyclic character of female reproduction and the non-cyclic nature of the male sex-activities may be explained.

The basophiles are being produced continually by the appearance of granules in the "basophilic" chromophobes, and just as constantly other basophiles are undergoing degranulation. The rate of differentiation and dedifferentiation is controlled by the gonad hormones. Since the basophiles of the male anterior lobe are less susceptible than those of the female to the control of the gonad hormones they are present in greater numbers and their output of pituitary hormone is greater. Removal of the gonads eliminates the control exerted by their hormone on the basophilic cycle with the result that there is not only a more rapid differentiation of basophiles, but also a failure to dedifferentiate and a tendency to enlarge and vacuolate. Coinciding with this basophilia there is an increased production of gonadotropic hormone. If gonad hormone is administered the cytological and physiological changes of castration can be prevented or abolished. Furthermore, if excessive amounts of gonad hormone are supplied to castrates, experimental cryptorchids, or normals the number of normal basophiles

and castration cells is markedly decreased (18, 19, 20). Furthermore, in long time castrates (6 to 12 months) of both sexes (25 males and 17 females) the writer has studied the effects of oestrin injections upon the hypophysis. Dosages as high as 50 R.U. daily for 40 days have been employed and it has been observed that the number of non-vacuolated basophiles had been decreased to a percentage lower than the normal average. The vacuolated castration cells were also markedly decreased, but never completely abolished. It is probable that longer periods of treatment will serve to eliminate them entirely.

With regard to the influence of the gonads upon the acidophiles little can be said at this time. They are decreased in size and number following gonadectomy, but a statement of the significance of that and other observations must await further study.

On the basis of the foregoing experimental evidence it is interesting to speculate upon the possible value of oestrin therapy in the treatment of pituitary basophilism, a hypophyseal disorder recently described by Cushing (21) with which there is associated a basophilic adenomata. If a causal relation actually exists between the basophilia and the clinical signs it is entirely conceivable that alleviative effects might be secured through properly controlled oestrin injections.

## THE CONTROL OF THE REPRODUCTIVE RHYTHMS

On the basis of the foregoing evidence it is possible to visualize certain factors which seem to be of importance in the control of the reproductive rhythms, and to offer a possible explanation for the occurrence of periodic sexual activity in the females and for the lack of periodicity in the male. The essential difference between the sex rhythms would seem to be due, in a large measure at least, to a fundamental difference in the reactivity of the male and female hypophyses to the suppressing influence of the gonads.

In the female the relatively low threshold for suppression by oestrin results in a diminished output of gonad-stimulating hormone whenever the oestrin content reaches a certain level. In the normal adult female the sequence of events becomes so adjusted that the oestrin level attains the threshold necessary for inhibition at fairly definite and regularly-spaced periods which are characteristic for any given species. Thus the hypophyseal activity which stimulates the gametogenic and endocrine processes of the ovary to induce ovulation and oestrus results in the secretion of sufficient oestrin to inhibit further production of gonadotropic hormone. In the course of events oestrus subsides, the oestrin level gradually falls, and a new cycle is initiated. In the event of pregnancy hypophyseal suppression persists and cyclic activity of the reproductive tract is held in abeyance throughout the gestation period.

The absence of a demonstrable sexual cycle in the male would seem to be accounted for on the basis of the higher threshold of gonad hormone required to inhibit the activity of the anterior lobe basophiles in the male.

Thus the male maintains continuous reproductive activity because the gonad hormone level never rises high enough to effect a temporary suppression of the hypophysis as it does in the female. It seems probable that in the normal male the activities of the hypophysis and the testes become so adjusted that they form a physiologically balanced system. That the suppression of the male hypophysis is far less extensive than that of the female is shown by the greater potency of male glands in gonadotropic hormone. Furthermore, the relative increase in gonadotropic potency following gonadectomy is more rapid in the female than in the male.

Attention should be called at this time to the lack of convincing evidence concerning the exact nature of the gonad hormone which controls the male hypophysis. That the testis is an essential factor is apparent, but no agreement exists concerning the principle through which the testis effects its control. Is it the same testis hormone that regulates the sex-accessories or is it a separate principle? Mottram and Cramer (22) were the first to suggest a second testicular hormone. Martins and Rocha (23) more recently have advanced a similar theory for the testicular control of the anterior lobe. Their evidence includes the study of experimental cryptorchid rats in which the hypophyses gradually undergo castration changes while the accessories remain normal, and the correction of castration changes in the hypophyses of gonadectomized rats by the administration of aqueous extracts of rat testes. The writer has attempted to confirm the latter experiments without success, and also has been able to show (24, 19) that the sex-accessories as well as the hypophyses undergo castration changes in cryptorchid rats providing sufficient time is allowed to elapse following the operation. It was suggested on the basis of these studies, and others upon the hypophyses and sex-accessories of vitamin E-deficient rats (25), that the results which seemed to warrant the postulation of a second hormone peculiar to the testis might be explained on the basis of difference in threshold levels for the action of a single testis-hormone on the hypophysis and sex-accessories.

Evidence is accumulating which points to the possibility of oestrin being a factor in the control of the male hypophysis. It is well known that oestrin may be extracted from testes and male urine, and recently Zondek (26) has shown that the testes and urine of stallions are the richest known sources of oestrin. The injection of pregnancy urine extracts in male rats results in an effect on the anterior lobe similar to that received with direct oestrin administration (19). In the treatment of gonadectomized rats with routine testis-hormone preparations containing traces of oestrin doses as low as 2 bird units daily for the female and 10 bird units for the male will prevent the appearance of castration changes in the hypophysis. Yet in a recent experiment with about 60 gonadectomized rats which were treated with testis extracts from which all oestrin had been removed it was found that double this amount was only partially effective.* From

*These experiments are being extended and will be considered later in conjunction with Dr. T. F. Gallagher.

the evidence that has been presented concerning the chemical natures of the testis-hormone and of oestrin it is not inconceivable that the former is transformed into the latter (Zondek, 27). The production of oestrin in the male would harmonize with the demonstration that it has a profound effect on the seminal vesicle musculature (28, 29).

The explanations offered for the control of the reproductive activities of the two sexes can be applied only to those animals which breed throughout the year. In seasonal breeders, both male and female, certain environmental factors appear to be concerned also in the control of the hypophysis and consequently of the sexual cycle. The nature of the pituitary-gonad relationship in a seasonal breeder will be discussed in another place.

### THE CONTROL OF THE MENSTRUAL CYCLE

It would seem possible to interpret the menstrual cycle in terms of the pituitary-gonad inter-relationship. The researches of Allen (30), Smith and Engle (31), and Hisaw, Meyer and Fevold (48) have established the importance of the ovarian hormones, oestrin and progestin, in the production of the premenstrual hyperplasia of the uterine endometrium. Their work has further shown that withdrawal of these hormones is followed by menstruation. It would seem probable that the sequence of events leading up to menstruation would be:

The withdrawal of the ovarian hormones incident to menstruation allows the anterior pituitary to secrete the gonad-stimulating hormone which in turn stimulates the maturation of a graafian follicle and the secretion of oestrin. During this period of follicular maturation the uterus undergoes repair and enters the interval phase. With attainment of maturity the follicle ruptures and a corpus luteum is formed. During the subsequent phases of the interval and the premenstruum the corpus luteum secretes oestrin and progestin, which together are responsible for the induction of endometrial proliferation. At the same time the increased production of oeostrin gradually suppresses the anterior pituitary with the result that production of gonadotropic hormone decreases. This allows the corpus luteum to undergo physiological regression, secretion of oestrin and progestin ceases, and menstruation occurs. The decline in oestrin secretion once more permits the anterior lobe to produce its hormone and a new cycle is initiated.

Fluhmann (46) has recently discussed the control of menstruation and has presented a description almost identical with the above analysis.

Consideration has been given to the relationship existing between the gonads and the hypophysis, the manner in which their reciprocal effects are exerted, and the resulting influence on the sex rhythms. In addition there are certain other physiological activities of the anterior lobe which appear to be influenced by the gonad hormones. These activities and the order in which they will be considered are lactation, carbohydrate metabolism, and growth.

### THE CONTROL OF LACTATION

That the development of the mammary glands depends upon the ovarian hormones has been adequately demonstrated (32, 33). The production of these hormones depends, of course, upon stimulation of the ovaries by the hypophysis. In all animals that have been studied the development of the mammary glands up to the incidence of the first pregnancy or, as is true in some forms, pseudopregnancy, is primarily, if not entirely, under the control of oestrin. In animals which have functional corpora lutea of ovulation the possibility exists that the corpus luteum hormone may have some effect on the mammary glands.

During pregnancy the mammary glands undergo complete development under the influence of oestrin and progestin. In some species, notably the guinea pig (34, 35), and possibly the monkey and man, oestrin alone in sufficient quantities is capable of inducing complete mammary development. In other animals progestin seems to be an essential factor in the production of the lobule alveolar development.

Although mammary gland proliferation is rapid and complete during pregnancy no milk is secreted. That the glands have the capacity to lactate has been shown by those instances in which the interruption of pregnancy has been followed by lactation. Normally the secretion products begin to collect in the alveoli during the later stages of pregnancy, but actual lactation is held in abeyance until after parturition. The factors which appear to be active in the inhibition of lactation during pregnancy have been discussed by the writer (36). It was shown by means of various surgical procedures that both the ovaries and the placenta are active in the inhibition of lactation, probably through the agency of oestrin. Furthermore, it was demonstrated that oestrin may inhibit the secretion of the lactogenic hormone by the anterior lobe (reciprocal effect), or it may act directly upon the mammary glands in the suppression of lactation (direct effect). It was possible by varying the experimental procedure, to show that both factors may be active during pregnancy, at least in the guinea pig.

More recent experiments have shown that the direct inhibition of lactation is a powerful factor. The injection of very potent, purified preparations of the lactogenic hormone into pregnant females (11 cases) has repeatedly failed to induce lactation or to in any way modify pregnancy. Less purified preparations induce lactation (15 cases), but only after the interruption of pregnancy. The response to the lactogenic hormone by male animals whose mammary glands had been completely proliferated through the agency of functional ovarian grafts (15 cases) or of oestrin injections (11 cases), parturient females (8 cases), and non-pregnant females (17 cases) has been inhibited by the simultaneous administration of oestrin.† However, this was shown to depend to some extent upon the relation of the amount of oestrin to the amount of lactogenic hormone supplied. For example male guinea pigs whose mammary glands had been

†The oestrin used in these experiments was an oil solution of Theelin which was kindly supplied by Dr. Oliver Kamm of Parke, Davis and Company.

developed by ovarian grafts were deprived of their grafts. This regularly resulted in copious lactation (8 animals). It was possible to inhibit lactation in such animals by the daily administration of as little as 30 rat units of oestrin. However, if lactogenic hormone was also administered lactation occurred (Fig. 5). When 100 rat units were injected daily it was impossible to obtain lactation with any amount of lactogenic hormone (Fig 6). Similar experiments have been conducted on parturient females. This would not only furnish evidence that oestrin may inhibit lactation, both through a suppression of the hypophysis and through a direct action on the mammary glands, but also indicates that the normal control of lactation depends upon a balanced relation between oestrin and the lactogenic hormone. During the period of high oestrin content during pregnancy lacta-

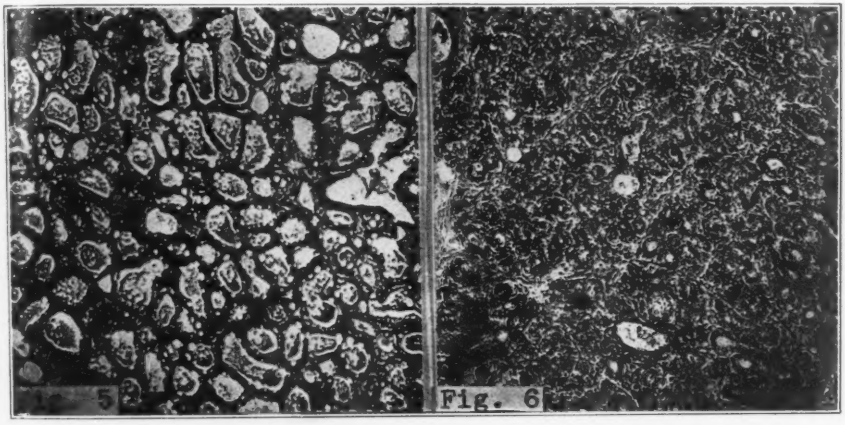



Figure 5. Mammary gland from male guinea pig 328. Animal had carried functional ovarian graft for 153 days. Injected for 8 days with a preparation of lactogenic hormone and 20 R.U. theelin daily. Note extensive lactation. x 104.

Figure 6. Mammary gland from male guinea pig 329. Litter-mate of 328. Also carried functional ovarian graft for 153 days. Injected with lactogenic hormone plus 100 R.U. theelin daily for 8 days. Note absence of lactation. x 104.

tion is held in check. With the decrease in oestrin at parturition the lactogenic hormone is secreted and as it finally overrides the inhibiting influences of oestrin on the mammary glands, induces the secretion of milk.

Selye, Collip, and Thomson (37) have presented evidence which they interpret as indicating the importance of a uterine influence upon the mammary glands during pregnancy. However, the uterus can hardly be considered as essential to the development of the mammary glands since complete mammary development and function can be induced in males and hysterectomized females. It is also held (38) on the basis of experiments on the rat that suckling sets up a reflex stimulation of the hypophysis to produce the lactogenic hormone, thus serving as an important factor in the maintenance of lactation. This concept was generally advanced in the older literature, but evidence has been advanced against it for the rabbit

(47) and the guinea pig (36). It is possible that a nervous participation in hormonal relations is more important in animals with very short cycles, e.g., the rat, than it is in other forms. It is believed that suckling exercises its most important function in the maintenance of lactation, in most forms at least, by removing the products of secretion.

### THE CONTROL OF EXPERIMENTAL DIABETES

Houssay's studies (39) have shown that there is a definite relationship between the anterior lobe and carbohydrate metabolism. Pancreatectomized dogs do not become diabetic if their hypophyses are also removed. However, if such animals are treated with anterior lobe extracts hyperglycemia and glycosuria ensue. There is some evidence that the thyroid and adrenals may be concerned in the relation of the pituitary to sugar metabolism, but whatever the intermediary factors may be the fact remains that the hypophysis does have a rôle in the metabolism of sugar.

The writer's experience with the action of oestrin in suppressing other pituitary functions suggested its use in an attempt to control experimental diabetes. This was successfully accomplished first in the dog (40). More recently these experiments have been extended to the rhesus monkey (41). It has been shown in two cases that hyperglycemia and glycosuria may be induced in normal monkeys by the injection of anterior lobe extract. In four animals the hyperglycemia and glycosuria which followed pancreatectomy has been abolished by the administration of theelin in oil (100-200 rat units daily). Withdrawal of the theelin was followed by a recurrence of the diabetic condition. Glycosuria was induced in animals receiving theelin when injections of anterior lobe extract were also given.

The results of these experiments are difficult to interpret in any way except that the administration of oestrin has suppressed the diabetogenic activity of the anterior pituitary. We are continuing and extending these studies.

### THE INFLUENCE OF THE GONADS ON GROWTH

Spencer, D'Amour, and Gustavson (42, 43) have reported that oestrin inhibits the growth of immature rats. Furthermore, the simultaneous injection of growth-promoting hormone and oestrin resulted in approximately normal growth. It would appear from this work that oestrin may suppress the growth-promoting activities of the anterior lobe.

Stein (44) has presented evidence which would indicate that a somewhat different relation may exist between the testis and growth. He observed that castrated rats grew less rapidly than their normal litter-mate brothers.

The relation of the gonads to growth has been discussed recently by Moore (45). It is apparent that, in spite of the literature on the subject, we are in need of carefully controlled studies on the effect of gonadectomy and gonad hormone injections upon body growth.

Very little can be said at this time concerning the action of oestrin on the cells believed to produce the growth factor, the acidophiles. Preliminary studies indicate that they, as well as the basophiles, undergo degranulation. Concerning the lactogenic and diabetogenic factors we are without knowledge of their exact relation to the anterior lobe cells. For that matter, it remains to be proven, particularly for the diabetogenic factor, that they are discrete hormones.

## SUMMARY AND CONCLUSIONS

The physiological inter-relations between the anterior hypophysis and the gonads are discussed and evidence gathered from numerous sources is summarized together with evidence presented previously by the writer and certain supplementary data.

Cell counts on the anterior lobes from 68 normal male and 56 normal female rats have shown that the male gland has a higher percentage of basophiles and acidophiles and a lower percentage of chromophobes than that of the female.

The anterior pituitaries from 25 castrate male and 17 spayed female rats which had been injected with oestrin showed a profound decrease in the percentage of both castration cells and non-vacuolated basophiles.

It is shown that the suppressing influence of the gonads on the gonadotropic activity of the hypophysis appears to be conducted through the action of the gonad hormones, particularly oestrin, on the secretory cycle of the anterior lobe basophiles. On the basis of physiological and histological evidence indicating a fundamental difference in the sensitivity to gonad hormone on the part of the male and female hypophysis an explanation is offered for the cyclic character of female reproduction and the absence of a cycle in the male. In the female the production of oestrogenic hormone attains periodically a concentration sufficient to suppress the production of gonadotropic hormone. As the production of oestrogenic hormone decreases with the lack of stimulation, the gonadotropic hormone is secreted again and a new cycle is initiated. In the male the hypophysis is less easily influenced by gonad hormone with the result that apparently it is never suppressed to the extent that the male reproductive functions exhibit cyclic characteristics.

It is shown that the pituitary-gonadal inter-relations also appear to be concerned in the control of certain other physiological processes. Oestrin seems to be related to the function of the mammary glands not only as a stimulus to mammary proliferation, but also by suppressing lactation. In guinea pigs—26 males whose mammary glands had been caused to proliferate through the agency of ovarian grafts or oestrin injections, eight parturient females, and 17 non-pregnant females—it was possible to promote or suppress lactation by varying the amounts of lactogenic hormone and oestrin which were administered.

Oestrin also has been shown to be active in the control of experimental pancreatic diabetes. In four monkeys the profound hyperglycemia and

glycosuria which followed pancreatectomy were abolished by the injection of oestrin.

It is concluded that the inter-relation between the anterior hypophysis and the gonads is an important factor in the control of the reproductive functions, including lactation. Experimentally it has been shown to be a possible factor in the control of carbohydrate metabolism and growth.

**REFERENCES**


1. Moore, C. R. and D. Price: Am. J. Anat. **50:** 13. 1932.
2. Kraus, E. J.: Beitr. z. path. Anat. u. z. allg. Path. **58:** 159. 1914.
3. Nelson, W. O.: Am. J. Anat. **52:** 307. 1933.
4. Severinghaus, A. E.: Anat. Rec. **57:** 149. 1933.
5. Wolfe, J. M., R. Cleveland and M. Campbell: Ztschr. f. Zellforsch. u. mikr. Anat. **17:** 420. 1933.
6. Addison, W. H. F.: J. Comp. Neurol. **28:** 441. 1917.
7. Engle, E. T.: Am. J. Physiol. **88:** 101. 1929.
8. Smith, P. E. and E. C. MacDowell: Anat. Rec. **50:** 85. 1931.
9. Bailey, P. and L. M. Davidoff: Am. J. Path. **1:** 185. 1925.
10. Biggart, J. H.: Bull. Johns Hopkins Hosp. **54:** 157. 1934.
11. Hohlweg, W. and M. Dohrn: Wien. Arch. f. inn. Med. **21:** 337. 1931.
12. Nelson, W. O.: Anat. Rec. **55:** 31. 1933.
13. Smelser, G. K.: Physiol. Zool. **6:** 396. 1933.
14. Rasmussen, A. T.: Anat. Rec. **29:** 394. 1925.
15. Rasmussen, A. T.: Anat. Rec. **55:** 34. 1933.
16. Rasmussen, A. T. and R. Herrick: Proc. Soc. Exper. Biol. & Med. **19:** 416. 1922.
17. Severinghaus, A. E.: Anat. Rec. **53:** 1. 1932.
18. Nelson, W. O.: Anat. Rec. **55:** 70. 1933.
19. Nelson, W. O.: Proc. Soc. Exper. Biol. & Med. **31:** 1192. 1934.
20. Severinghaus, A. E.: Proc. Soc. Exper. Biol & Med. **31:** 593. 1934.
21. Cushing, H.: Pituitary body, hypothalamus, and parasympathetic nervous system. Charles C. Thomas, Springfield, Ill. 1932.
22. Mottram, J. C. and W. Cramer: Quart. J. Exper. Physiol. **13:** 209. 1923.
23. Martins, T. and A. Rocha: Endocrinology, **15:** 421. 1931.
24. Nelson, W. O.: Anat. Rec. **58:** 30. 1934.
25. Nelson, W. O.: Anat. Rec. **56:** 241. 1933.
26. Zondek, B.: Nature, **133:** 209. 1934.
27. Zondek, B.: Nature, **133:** 494. 1934.
28. Freud, J.: Biochem. J. **27:** 1438. 1933.
29. Overholser, M. D. and W. O. Nelson: Anat. Rec. **58:** 31. 1934.
30. Allen, E.: The ovarian follicular hormone, theelin; animal reactions. Chapter 9, Sex and Internal Secretions. Williams and Wilkins Co., Baltimore. 1932.
31. Smith, P. E. and E. T. Engle.: Proc. Soc. Exper. Biol. & Med. **29:** 1225. 1932.
32. Turner, C. W. and W. U. Gardner: Missouri Agric. Exper. Sta. Res. Bull. No. 158. 1931.
33. Nelson, W. O.: Anat. Rec. **60:** 69. 1934.
34. Nelson, W. O.: Anat. Rec. **54:** 51. 1932.
35. Nelson, W. O. and G. K. Smelser: Am. J. Physiol. **103:** 374. 1932.
36. Nelson, W. O.: Endocrinology, **18:** 33. 1934.
37. Selye, H., J. B. Collip and D. L. Thomson: Endocrinology, **18:** 237. 1934.
38. Selye, H. and T. McKeown: Proc. Soc. Exper. Biol. & Med. **31:** 683. 1934.
39. Houssay, B. A. and A. Biasotti: Endocrinology, **15:** 511. 1931.
40. Barnes, B. O., J. F. Reagan and W. O. Nelson: J. A. M. A. **101:** 926. 1933.
41. Nelson, W. O. and M. D. Overholser: Proc. Soc. Exper. Biol. & Med. (In press.)
42. Spencer, J., F. E. D'Amour and R. G. Gustavson: Am. J. Anat. **50:** 129. 1932.
43. Spencer, J., F. E. D'Amour and R. G. Gustavson: Endocrinology, **16:** 647. 1932.
44. Stein, S. J.: Anat. Rec. **56:** 15. 1933.
45. Moore, C. R.: The biology of the testis. Chapter 7. Sex and Internal Secretions. Williams and Wilkins Co., Baltimore. 1932.
46. Fluhmann, C. F.: A modern theory of menstruation. Northwest Med. **33:** 10. 1934.
47. Hammond, J. and F. H. A. Marshall: Reproduction in the rabbit. Oliver and Boyd. Edinburgh. 1925.
48. Hisaw, F. L., R. K. Meyer and H. L. Fevold: Proc. Soc. Exper. Biol. & Med. **27:** 400. 1930.

# THE CONCENTRATION OF GONAD-STIMULATING HORMONE IN BLOOD SERUM AND OF OESTRIN IN THE URINE THROUGHOUT PREGNANCY IN THE MARE*

H. H. COLE AND F. J. SAUNDERS
*College of Agriculture, University of California*
DAVIS

Cole and Hart (1930 and 1930a) have shown that the blood serum of mares contains a gonad-stimulating hormone between the 45th and the 150th days and small amounts of oestrin during the last half of pregnancy. According to Zondek (1930), tremendous amounts of oestrin are present in the urine of the mare between the 74th and 260th days. The concentration of these hormones at the various stages of pregnancy has not, however, been systematically studied. Many problems might be more easily solved if exact information on this point were available. For example, one question concerns the sources of these hormones. Does the fetus with its attending membranes initiate an unusual activity of the hypophysis and ovary or are the hormones in question vicariously produced during this phase of reproduction? Another problem concerns the fate of the gonad-stimulating hormone. It is not excreted in the urine unchanged for only rarely can it be detected there. Thus it must be eliminated with other body excretions or destroyed within the mare. In addition, several interesting gonadal phenomena characteristic of this species may be partly explained by a study of hormonal concentrations. Another objective in our experiments was to ascertain in what period of gestation these hormones are most abundant.

In this study we have not attempted to fractionate the serum into several components having specific ovarian effects. Publications by Fevold, et al. (1931), Leonard (1931), and Evans, et al. (1931), indicate that such an investigation might be fruitful. Our tests have shown, however, that at all stages of pregnancy in which the serum gives an ovarian response it will bring about the maturation of follicles, oestrus, ovulation, and the development of normal corpora lutea in the rat, mouse, sow, cow, and ewe. Furthermore, some, at least, of these phenomena may be produced in the bitch, rabbit, and mare.†

We have taken frequent samples, therefore, from a few individuals and have studied the concentration of gonad-stimulating hormone and oestrin. This paper will not discuss in detail the theoretical considerations pertaining to the source of these two hormones or to the disposition of the former, but may serve in the direct attack upon these attractive problems.

*Read in part before the Eighteenth Annual Meeting of the Association for the Study of Internal Secretions, Cleveland, June 11, 1934.

†We have very recently found a prolan-like substance, recognized by means of the pituitary synergistic factor, in the blood of the mare at the 30th day of pregnancy. Its presence coincidentally with the gonad-stimulating hormone after the 40th day has likewise been demonstrated.

### MATERIAL AND METHODS

We have studied the concentration of both gonad-stimulating hormone and oestrin in two Thoroughbred mares, C6 and C8, throughout pregnancy. In a draft mare, C3, the concentration of gonad-stimulating hormone was studied from the 96th to the 176th day; that of oestrin from the 104th day until after parturition. In another draft mare, C4, whose fetus was apparently resorbed, the concentration of gonad-stimulating hormone was followed, and the urine was examined for oestrin. The blood samples were collected in sterile flasks by tapping the jugular vein. After the blood had stood for a few hours, the supernant serum was drawn off and was stored at 5° C. until tested. During the early part of pregnancy, samples were drawn every two days from two mares and at longer intervals from the other two (Table 1). The amount of blood drawn was kept to a minimum

TABLE I

THE CONCENTRATION OF GONAD-STIMULATING HORMONE IN THE BLOOD SERUM OF THE PREGNANT MARE

| Mare C6 | | Mare C8 | | Mare C3 | | Mare C4* | |
|---|---|---|---|---|---|---|---|
| Day of Pregnancy | Rat Units Per Liter | Day of Pregnancy | Rat Units Per Liter | Day of Pregnancy | Rat Units Per Liter | Day of Pregnancy | Rat Units Per Liter |
| 43 | <60 | 43 | <100 | | | | |
| 45 | 500 | 45 | 390 | | | | |
| | | 47 | 1,562 | | | | |
| 49 | 6,250 | 49 | 3,125 | | | 49 | 6,250 |
| 51 | 12,500 | | | | | | |
| 53 | 25,000 | 53 | 25,000 | | | | |
| 55 | 25,000 | 56 | 50,000 | | | | |
| 57 | 50,000 | | | | | | |
| 59 | 50,000 | 60 | 50,000 | | | | |
| 61 | 50,000 | 64 | 50,000 | | | 62 | 25,000 |
| 65 | 50,000 | | | | | | |
| 69 | 50,000 | 70 | 50,000 | | | | |
| 73 | 50,000 | 74 | 50,000 | | | 72 | 12,500 |
| 75 | 50,000 | | | | | | |
| 77 | 50,000 | | | | | | |
| 79 | 50,000 | | | | | | |
| 83 | 50,000 | 82 | 50,000 | | | 83 | 6,250 |
| 87 | 25,000 | 86 | 50,000 | | | | |
| 91 | 50,000 | 94 | 50,000 | | | 92 | 1,562 |
| 95 | 25,000 | | | 96 | 25,000 | | |
| 103 | 25,000 | 102 | 50,000 | 105 | 12,500 | 102 | 1,562 |
| | | 110 | 50,000 | | | | |
| 111 | 12,500 | | | 114 | 6,250 | 112 | 781 |
| 119 | 6,250 | 119 | 12,500 | | | | |
| 128 | 3,125 | 126 | 12,500 | 125 | 3,125 | 122 | 400 |
| 135 | 1,562 | 134 | 6,250 | 135 | 1,562 | 132 | 200 |
| 143 | 781 | 142 | 3,125 | 145 | 781 | 143 | 100 |
| | | 149 | 1,562 | | | | |
| 151 | 390 | | | 155 | 400 | | |
| 158 | 390 | | | | | | |
| 167 | 100 | 167 | 100 | 165 | 400 | | |
| 176 | 390 | | | 176 | 100 | | |
| 185 | <100 | 181 | 100 | | | | |
| 208 | <50 | 198 | <50 | | | | |

*Mare C4 did not give birth to a foal. The fetus was undoubtedly resorbed.

in order that its removal might not interfere appreciably with the normal hormonal concentrations. Later, when the level of gonad-stimulating hormone in the blood was changing less rapidly, the intervals between samplings were extended to from 4 to 10 days.

In this work a rat unit of gonad-stimulating hormone was defined as the amount that would produce, in a group of four rats, an average of from three to ten mature follicles or corpora; and half of which would not produce this average in another group of four rats. This method of assay is very similar to that suggested by Cole, Guilbert, and Goss (1932), except that four rats instead of six were used at each level in order to reduce somewhat the very considerable number of animals required. Preferably, of course, more rats would be employed at each level; but the accuracy of the tests was not seriously affected by the use of four instead of six. The serum was administered in a single subcutaneous injection into 25-day-old rats, which were autopsied on the fifth day thereafter. This method obviates the weighing of the ovaries. At least eight rats were needed for each test, and usually twelve or more were used.

The urine was sampled by catheterizing the mares at midday. Its oestrin content was determined by the use of spayed rats, to which it was administered in three equal-sized doses given at 8 a.m., at 4 p.m., and at 8 a.m. on the following day. Where necessary, it was diluted so that at least ½ cc. of dilute was injected to minimize the errors of measurement. Vaginal smears were taken at 56 and 72 hours after the initial injection. In this work a rat unit of oestrin was defined as the minimal amount necessary to cause a positive vaginal response in at least three of the four rats injected at this level. The reaction was considered as positive when the smear consisted of nucleated or cornified epithelial cells, or both, and was free of leucocytes.

### GONAD-STIMULATING HORMONE

After gonad-stimulating hormone is first recognized in the blood stream, its production is surprisingly rapid (Fig. 1). For two mares we have very exact information on this point. In both cases, C6 and C8, 10 cc. of serum failed to give a positive response on the 43rd day. On the 45th day, about 2 cc. gave a positive response. Twelve days later, 0.02 cc. represented a rat unit in both cases (Table 1). As a 1,100-pound mare has about 19 liters of blood serum, about one million rat units have been produced over a twelve-day period. This calculation does not take into account the very considerable amounts of hormone present in the maternal and fetal placenta. In instances reported by Catchpole and Lyons (1934), the maternal endometrium of a single mare contained over 100,000 rat units. There is indubitable evidence that the hormone is formed faster as the concentration increases, until the level of at least 50,000 rat units per liter is reached. Above this point we have no definite evidence to show whether or not the concentration rapidly comes to a maximum or whether

the rate of production decreases as this maximum is approached.* With mare C8, however, the reaction obtained at 70 days indicates that the concentration had reached a maximum closely approximating 100,000 R.U. per liter. Judging from Figure 1, the concentration remained at a maximum level for a considerable period. The curve obtained may be explained on the following basis: The rise in concentration follows the curve of an autocatalytic reaction. As the concentration increases, the elimination or destruction of the hormone is probably increased until the rate of production equals the rate of elimination and the concentration remains approximately constant. Apparently there is a time when the production suddenly ceases, and the decrease in concentration then follows the same course as a diffusion curve or the curve for a monomolecular reaction (Fig. 2). The concentration is reduced one-half every 8 to 10 days. As the

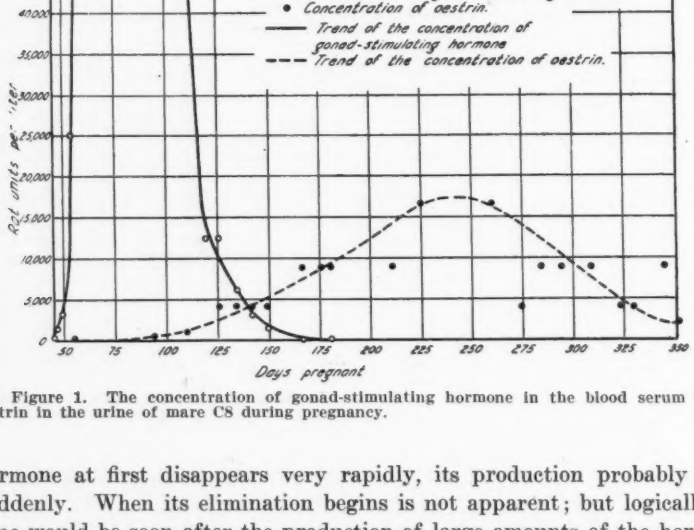



Figure 1. The concentration of gonad-stimulating hormone in the blood serum and of oestrin in the urine of mare C8 during pregnancy.

hormone at first disappears very rapidly, its production probably stops suddenly. When its elimination begins is not apparent; but logically the time would be soon after the production of large amounts of the hormone.

Inasmuch as the typical growth curve is also sigmoid, the speeding up of production as the amount of hormone increases might be explained by secretory tissue growth. Catchpole and Lyons (1934) have suggested that the allantochorionic cells secrete this hormone. As these cells are proliferating rapidly at this time, there is some justification for the view that more rapid production of the hormone depends upon an increase in the amount of secreting tissue.

*With our present method of assay of the hormone, the doses used are multiples of two. Although the relative error is the same regardless of hormone concentration, the absolute error is unfortunately greater at the higher levels. For example, we can distinguish between 100 and 200 R.U. per liter but not between 25,000 and 37,500.

In the cases described above, the concentration of gonad-stimulating hormone per liter does not exceed 50,000 R.U. or, to be more exact, does not reach 100,000 R.U. The two mares, C6 and C8, which were followed throughout the period, were mother and daughter. In another mother-and-daughter combination the hormone concentration was well above 100,000 R.U. per liter. The possibility of hereditary differences in this particular is therefore suggested.

Assay of gonad-stimulating hormone: One of the limitations of our method of assay used in connection with the data just presented is that increases in concentration of less than 100 per cent are not recognized. We realize that intermediate levels might be recognized by the use of a larger number of rats. However, our experience with the effect of increasing dosages of mare serum upon the ovary weight led us to believe that

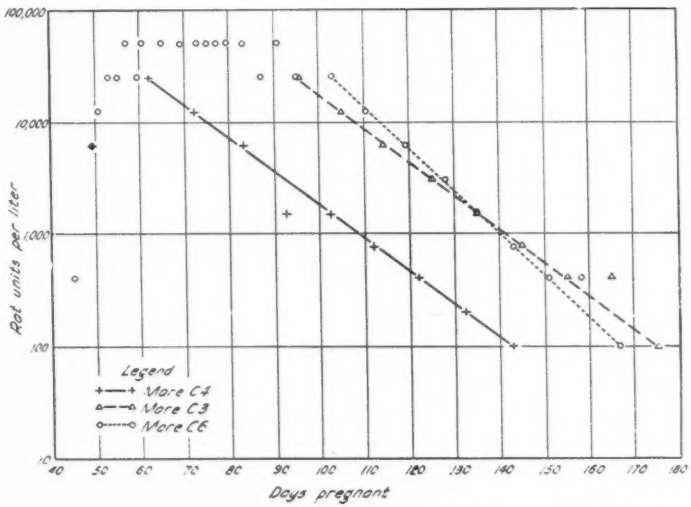



Figure 2. The logarithm of the concentration of the gonad-stimulating hormone plotted against time.

possibly a more accurate method of assay might be devised which would actually use fewer instead of more rats. Therefore a number of serums and extracts of serums, have been tested to determine the effect of different dosages upon the ovarian weight of immature rats. First, the number of rat units in the serum was determined by our old method of assay; i.e., the dose of serum was halved until the minimal amount was found which would produce an average of at least 3 corpora per rat in a group of six rats. Then with this figure as a basis increasing amounts were administered to determine if a constant relationship was maintained between ovary weight and the minimal reaction while using different serums. If so, the ovary weight could be used in assaying the hormone. A fairly close relationship does exist between the ovary weight and the minimal

## TABLE II

THE EFFECT OF INCREASING DOSAGES OF THE GONAD-STIMULATING HORMONE OF MARE SERUM UPON THE OVARIES OF IMMATURE RATS AND THE SIGNIFICANCE OF THE DIFFERENCES BETWEEN MEAN OVARIAN WEIGHTS

| Rat Units* Injected | Serum VII | | Serum IV | | Serum VI | | Serum Extract 24 | | Serum Extract 25 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Ovary† Weights | P‡ | Ovary Weights | P | Ovary Weights | P | Ovary Weights | P | Ovary Weights | P |
| 0.5 | mgm. 18 | | mgm. | | mgm. 21 | | mgm. 20 | | mgm. 17 | |
| 1 | 20 | 0.5 <P<0.6 | 19 | | 24 | 0.3 <P<0.4 | 25 | 0.05<P<0.1 | 23 | 0.02<P<0.05 |
| 2 | 23 | 0.2 <P<0.3 | 24 | 0.02<P<0.05 | 25 | 0.5 <P<0.6 | 26 | 0.1 <P<0.2 | 28 | 0.02<P<0.05 |
| 4 | 26 | 0.2 <P<0.3 | 30 | <0.01 | 28 | 0.3 <P<0.4 | 34 | 0.01<P<0.02 | 35 | 0.02<P<0.05 |
| 8 | 43 | <0.01 | 37 | 0.4 <P< .05 | 55 | <0.01 | 80 | <0.01 | 64 | <0.01 |
| 16 | 66 | 0.01<P<0.02 | 75 | 0.05<P<0.1 | 105 | <0.01 | 120 | 0.01<P<0.02 | 114 | <0.01 |
| 32 | 118 | <0.01 | 127 | 0.02<P<0.05 | 117 | 0.3 <P<0.4 | 134 | 0.2 <P<0.3 | 135 | 0.3 <P<0.4 |
| 64 | 137 | 0.1 <P<0.2 | 194 | <0.01 | 186 | <0.01 | 210 | <0.01 | | |
| 128 | 169 | 0.1 <P<0.2 | 218 | 0.3 <P<0.4 | 243 | 0.05<P<0.1 | | | | |

*The number of rat units in each serum was first determined by halving the dose until the minimal amount was found which would produce an average of from 3 to 10 mature follicles or corpora in immature rat ovaries.

†Eight rats were used at each level for Serum VII; for the other serums listed only six were used.

‡When "P" is 0.05 or less the difference between the means may be considered as significant. See Fisher, Statistical Methods for Research Workers, 4th Edition.

amount to mature an immature rat when untreated mare serum or acetone-ammonia preparations of the serum are used. Six rats were used at each dosage level for each serum with the exception of Serum VII, in which case 8 were used. It will be observed from Table 2 that when the dose is doubled there is only a comparatively narrow range over which significant difference between the means are found. For example, if the ovary weights of rats receiving ½ and 1 rat unit are compared, significant differences are rarely found when 6 or 8 rats are injected at each level. The same is true in general when 1 and 2 or 2 and 4 rat units are compared. In fact, these insignificant differences between ovary weights when the dose was doubled at lower levels led us originally to adopt the method of comparing corpora and ripe follicles in preference to difference in ovary weight in assaying for gonad-stimulating hormone. However, the need for a more accurate method of assay without involving the use of more rats brought up again the possibility of comparing ovary weights. As may be seen in Table 2, when ovary weights of rats receiving 4 and 8 or 8 and 16 rat units are com-

TABLE III

THE SIGNIFICANCE OF THE DIFFERENCES BETWEEN MEAN OVARIAN WEIGHTS OF RATS RECEIVING VARYING DOSAGES OF SERUM VII

| Dosages Compared (Rat Units) | Mean Ovarian Weights of Eight Rats at Each Dosage Level | Value of T* | Value of P* |
|---|---|---|---|
| ½ and 1 | 18 and 20 | 0.6 | 0.5 <P<0.6 |
| 1 and 2 | 20 and 23 | 1.3 | 0.2 <P<0.3 |
| 2 and 4 | 23 and 26 | 1.1 | 0.2 <P<0.3 |
| 4 and 6 | 26 and 39 | 3.4 | <0.01 |
| 4 and 6 (Duplicate) | 28 and 38 | 3.8 | <0.01 |
| 4 and 8 | 26 and 43 | 5.2 | <0.01 |
| 4 and 8 (Duplicate) | 28 and 44 | 14.0 | <0.01 |
| 6 and 8 | 39 and 43 | 1.0 | 0.3 <P<0.4 |
| 6 and 8 (Duplicate) | 38 and 44 | 1.5 | 0.1 <P<0.2 |
| 6 and 12 | 39 and 66 | 3.0 | <0.01 |
| 8 and 12 | 43 and 66 | 2.7 | 0.01<P<0.02 |
| 8 and 12 (Duplicate) | 44 and 64 | 3.7 | <0.01 |
| 8 and 16 | 43 and 66 | 2.7 | 0.01<P<0.02 |
| 8 and 16 (Duplicate) | 44 and 80 | 3.0 | <0.01 |
| 12 and 16 | 66 and 66 | | |
| 12 and 16 (Duplicate) | 64 and 80 | 1.3 | 0.2 <P<0.3 |
| 12 and 24 | 66 and 145 | 6.7 | <0.01 |
| 16 and 24 | 66 and 145 | 6.7 | <0.01 |
| 16 and 24 (Duplicate) | 80 and 111 | 1.6 | 0.1 <P<0.2 |
| 16 and 32 | 66 and 119 | 5.2 | <0.01 |
| 32 and 64 | 119 and 137 | 1.4 | 0.1 <P<0.2 |
| 64 and 128 | 137 and 169 | 1.6 | 0.1 <P<0.2 |

*For "T" and "P" see Fisher, Statistical Method for Research Workers, 4th Edition. When "P" is 0.05 or less the difference may be considered as significant.

pared highly significant differences are nearly always found. Further, the data in Table 3 show that a 50 per cent increase in dose gives a significant increase in ovary weight over this range when eight rats are used at each level (see 4 and 6, 8 and 12, or 16 and 24 rat unit levels). A 33 1/3 per cent increase in dose, does not show significant differences (see 6 and 8, or 12 and 16 rat unit levels).* When amounts greater than 16 rat units are given the ovary weight cannot be used in assaying for the hormone as significant differences between the means are no longer regularly found.

In proposing a method of assay for the gonad-stimulating hormone of mare serum, we will use the data on Serum VII given in Table 3, in which 16 rats were used at the levels concerned. We suggest, therefore, that the following range of ovary weights obtained by injecting eight rats with a single subcutaneous dose on the 25th day of age with autopsy 120 hours later be assigned the following values in rat units:

| Ovary Weight in mgm. | Rat Unit Value |
|---|---|
| 33 to 41 | 6 |
| 42 to 54 | 8 |
| 55 to 69 | 12 |
| 70 to 100 | 16 |

We realize that this method of assay cannot be used without modification for gonad-stimulating hormone derived from other sources such as the pituitary or pregnancy urine. However, the rat unit values obtained are comparable to those of other methods based on the minimal amount necessary to mature the ovary of the immature rat.

### OESTRIN

Oestrin appears in the urine of the mare in appreciable amounts at about the 100th day of pregnancy (Table 4)—the time when the concentration of gonad-stimulating hormone begins to fall. In one instance, C8, traces were detected as early as the 54th day. Zondek (1930) found tremendous amounts between the 74th and the 260th days. According to our results, however, the hormone does not become concentrated in the urine until about the 150th day, and its highest concentration is found between the 200th and the 275th days. The marked difference between the number of units reported by Zondek and by us results, no doubt, entirely from the method of assay. He used mice instead of rats and gave more frequent injections than did we. After the 275th day the hormone level in the urine gradually falls off. During the last two months of pregnancy, we have followed the oestrin level in the urine of three other mares in addition to those given in Table 4; and in all these cases the drop in the oestrin level was similar to that of mare C8 in Table 2. Apparently, when the interval of pregnancy is unusually long, as in mare C6, the oestrin concentration is very low at the time of parturition. Catchpole and Cole (1934) have reported elsewhere on the disappearance of oestrin in the urine about the

*Even though the duplicate groups are united and the average ovarian weights of sixteen rats are compared significant differences are not found by a 33⅓ per cent increase in dose.

TABLE IV

THE CONCENTRARION OF OESTRIN IN THE URINE OF THE PREGNANT MARE

| Mare C6 | | Mare C8 | | Mare C3 | |
|---|---|---|---|---|---|
| Day of Pregnancy | Rat Units Per Liter | Day of Pregnancy | Rat Units Per Liter | Day of Pregnancy | Rat Units Per Liter |
| 63 | <125 | 54 | 261 | | |
| 79 | <125 | 70 | <521 | | |
| | | 94 | 521 | | |
| 103 | 2,083 | 110 | 1,041 | 104 | 333 |
| 119 | 4,167 | 126 | 4,167 | 113 | 333 |
| 135 | 4,167 | 134 | 4,167 | 124 | 667 |
| 143 | 8,333 | 142 | 4,167 | 133 | 1,667 |
| | | 149 | 4,167 | 144 | 1,667 |
| 151 | 8,333 | 158 | 8,333 | 154 | 1,667 |
| 158 | 16,667 | 167 | 8,333 | 164 | 3,333 |
| 167 | 8,333 | | | 175 | 3,333 |
| 176 | 8,333 | 176 | 8,333 | 185 | 5,000 |
| 190 | 8,333 | 181 | 8,333 | 194 | 5,000 |
| 207 | 16,667 | 211 | 8,333 | 206 | 33,333 |
| 220 | 16,667 | 225 | 16,667 | 221 | 33,333 |
| 234 | 8,333 | | | 245 | 8,333 |
| | | 260 | 16,667 | | |
| 270 | 8,333 | 274 | 4,167 | 279 | 16,667 |
| 284 | 4,167 | 281 | 8,333 | 294 | 8,333 |
| 291 | 4,167 | 295 | 8,333 | | |
| 305 | 1,041 | 309 | 8,333 | 308 | 8,333 |
| 319 | 2,083 | 323 | 4,167 | 322 | 4,167 |
| 326 | 2,083 | 330 | 4,167 | | |
| 340 | 2,083 | 344 | 8,333 | | |
| 354 | 1,041 | | | | |
| 361 (1 day before foaling) | 261 | 352 (1 day before foaling) | 2,083 | | |
| 2 days after foaling | <200 | 8 days after foaling | <132 | 1 day after foaling* | <84 |

*Foaled on 334th day.

time of foaling. The cases studied here agree with those previously described. In other words, oestrin may be found in the urine up to the time of foaling; but within a day or two thereafter the level drops to a point where the hormone can no longer be detected in untreated urine.

In mare C4, in which a resorption of the fetus probably began during the first 100 days of pregnancy, only traces of oestrin were encountered in the urine on the 112th and 153rd days after breeding (3 cc. of urine gave a positive vaginal response on the first and 5 cc. on the second date). Between the 62nd and the 200th day after breeding, thirteen tests were run for oestrin at approximately ten-day interval. Clearly, the production of oestrin in large amounts in the mare depends upon the presence of a living fetus. In view of this fact, together with other unpublished data and the findings of Catchpole and Cole (1934), it seems highly improbable that the maternal ovary ever contributes appreciably, at any stage of pregnancy, to the production of the enormous amounts of oestrin excreted in the urine and fetus of the mare.

## SUMMARY

The concentrations of gonad-stimulating hormone in the serum have been determined in four and those of oestrin in the urine in three mares

throughout pregnancy. Gonad-stimulating hormone is produced very rapidly after its first appearance in the blood, the rate increasing with the concentration up to a certain point. The curve representing the concentration of the hormone during the production period is sigmoid, and its similarity to the growth curve has been noted. The hormone apparently reaches its highest level in the serum at about the 70th day. The curve representing its rate of disappearance resembles a diffusion curve or the curve for a monomolecular reaction. The concentration is reduced one-half every 8 to 10 days. In one mare, the fetus of which was resorbed, gonad-stimulating hormone disappeared at a rate similar to that in the other mares studied.

A method of assay of gonad-stimulating hormone based on the ovary weights of immature rats is presented.

It was found that oestrin appears in the urine of the mare at about the 100th day of pregnancy. The highest concentration was found between the 200th and the 275th days. Thereafter, the concentration gradually declined, so that by the time of parturition 0.24 cc. or more of urine had to be given to produce a response. A day or two after parturition, oestrin could no longer be detected in the urine.

## REFERENCES

Catchpole, H. R. and H. H. Cole: Anat. Rec. **59:** 335. 1934.
Catchpole, H. R. and W. R. Lyons: Am. J. Anat. **55:** 167. 1934.
Cole, H. H. and G. H. Hart: Am. J. Physiol. **93:** 57. 1930.
Cole, H. H. and G. H. Hart: Am. J. Physiol. **94:** 597. 1930a.
Cole, H. H., H. R. Guilbert and H. Goss: Am. J. Physiol. **102:** 227. 1932.
Evans, H. M., K. Meyer and M. E. Simpson: Proc. Soc. Exper. Biol. & Med. **28:** 845. 1931.
Fevold, H. L., F. L. Hisaw and S. L. Leonard: Am. J. Physiol. **97:** 291. 1931.
Leonard, S. L.: Am. J. Physiol. **98:** 406. 1931.
Zondek, B.: Klin. Wchnschr. **9:** 2285. 1930.

# A CASE OF PITUITARY INFANTILISM TREATED WITH COMMERCIAL ANTERIOR PITUITARY PREPARATIONS

GEORGE B. DORFF, M.D.
*From the Endocrine Clinics of the Department of Pediatrics of New York University and Medical College and of Bellevue Hospital*
BROOKLYN, N. Y.

Pituitary infantilism is no rarity. However, the treatment of such cases is still in the experimental stage, hence interest attaches to any success achieved.

H. N., a boy, aged 16 years, was admitted to the Endocrine Clinic on March 22, 1932. His presenting complaints were dwarfism, lack of genital development and asthma. His childhood diseases were measles, pertussis, mumps, occasional colds, and "bronchial asthma" since the age of three years. There was no history of a delay in teething, walking or talking. His growth, however, was slow. He has one brother ten years of age who is about the same size as the patient. The latter at the time of first contact was attending the third grade at high school. He was particularly troubled about the fact that he had not been able to gain in height or weight for the preceding few years.

*Physical Examination.* The boy was thin, poorly nourished, and dwarfed. He presented an alert, youthful and anxious expression. His height was 57 inches (the average normal being 61.8-66.2) and he weighed 63 pounds (the average normal being 96-122). His chest was emphysematous in type and showed the presence of many musical rales throughout. His heart showed no evidence of any adventitious sounds. There was a nasal purulent discharge in the right nostril, and his throat was granular. All his permanent teeth were present and in good condition. His vision was normal. A Mantoux test 1/100 was negative.

His genitalia showed the presence of two small testes in the scrotum. The penis was small and there were a few fine, fuzzy pubic hairs. The appearance of the patient was eunuchoid in type—the lower measurement was 30 inches and exceeded the upper.

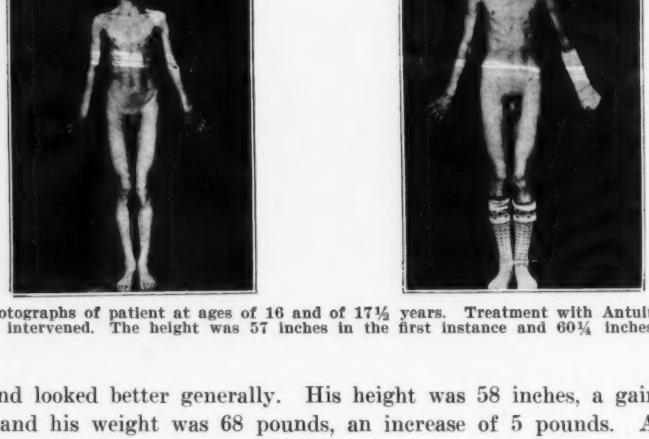
*Roentgenographic examinations* on March 24, 1932, showed a moderate degree of emphysema and bronchitis of both lungs. The heart was hypoplastic. The skull was well formed and seemed rather large for a patient of this age; there were no destructive or productive changes of the bone entering into its formation. The sella turcica was within normal limits. The ethmoids, particularly the posterior group, left antrum, and the sphenoidal sinus region were rather cloudy.

The bones of the upper and lower extremities were small but well formed. There were eight carpals present of fairly good size, although

the massing was not quite up to his age. The epiphyses of the phalanges, metacarpals and distal radius and ulna were open. The trochlea was small and not united with the capitellum. The olecranon was present, and small. The epiphysis of the head of the radius was open. The epiphyses of the external and internal condyles were not united to the humerus. The epiphyses of the distal tibia and fibula were widely open, and the upper segment of the epiphysis of the os calcis was widely separated while the lower was more approximated to the bone.

A *diagnosis* of anterior pituitary infantilism of the Levi-Lorain type was made and the patient was placed on Antuitrin (Parke, Davis & Co.), 1 cc. three times a week hypodermically, in addition to some anterior pituitary extract in small doses, orally.

By June 14, 1932, three months later, the patient had received about 43 injections of Antuitrin, and about 26 ultra violet ray treatments. He



Photographs of patient at ages of 16 and of 17½ years. Treatment with Antuitrin and Phyone intervened. The height was 57 inches in the first instance and 60¼ inches in the latter.

felt and looked better generally. His height was 58 inches, a gain of 1 inch, and his weight was 68 pounds, an increase of 5 pounds. At this point Antuitrin was discontinued.

In October, 1932, four months later, Phyone (The Wilson Laboratories) was instituted ranging from 0.5 to 1 cc., three times a week, of which he received about 30 cc. by January, 1933. His height at the beginning of the Phyone treatment was 58 inches, his weight was 67 pounds, and his lower measurement was 31¼ inches (the height was the same as in June at the end of the Antuitrin injections). After three months of Phyone therapy, in January, 1933, he contracted influenza and was subsequently sent to the country for his convalescence. All hypodermic medication was discontinued at this point.

The patient was not seen again until one year later, in September, 1933, at which time his height was 60¼ inches and his weight was 74½

pounds, a total gain of 3¼ inches in height and 11½ pounds in weight in 18 months, subsequent to the institution of Antuitrin and Phyone. The genitalia showed a remarkable improvement, in that the two hypoplastic testes and the penis were markedly increased in size. There was present a marked crop of long black pubic hair and his entire general makeup had become more mature.

The patient thinks that most of his gain in height occurred between January and July, 1933, and that his genital change occurred between March and June of the same year. He had had two accidents during this year and had fractured his radius and ulna on both of these occasions at practically the same sites. Examination of the x-ray plates of May 5, 1933, showed the fractures as indicated. There were, in addition, eight carpals of fairly good size, although the epiphyses of the ulna and radius, phalanges and metacarpals were still open. It is of interest also to note that the patient had gained about 20 pounds in weight since the attack of influenza—an increase so great had never occurred before. However, he had had many severe attacks of asthma during the summer of 1933 and he lost some of this weight which he had gained. It is of interest to note that his asthma improved somewhat coincident with the gland treatment.

## COMMENT

A diagnosis of pituitary infantilism of the Levi-Lorain type was based on the following findings: a shortness of stature, underweight, genital hypoplasia and a delay in bone development as evidenced by a delay in the closure of certain of the epiphyses.

The eunuchoid proportions seen in this case were rather unusual, but not exceptional, for they have been seen by the writer to occur occasionally in cases of dwarfism. However, primary hypogenitalism can be ruled out, for subjects of this disorder are tall and often characteristically obese with the trunk-leg ratio reversed, rather than stunted in height. Unfortunately, a basal metabolic rate determination could not be obtained. However, it is felt that this case would not fall within the hypothyroid classification for there was rapidity of pulse, alertness of expression, normal mentality and not in sufficient degree the retardation in the appearance of the ossification centers and epiphyseal nuclei that are found in such dwarfism.

Of interest is the fact that this boy's height remained stationary for a number of years and that under treatment with the commercial anterior pituitary growth-stimulating preparations he made his first rapid advance. On Antuitrin he gained 1 inch and then on Phyone he grew another 2¼ inches, or 3¼ inches in eighteen months. In addition, at the age of 17 years (less than 1 year after entering the Endocrine Clinic) puberal changes took place. That delay in puberty would have terminated, and puberal changes would have occurred naturally, if treatment had not been given, must be considered; however, this is improbable because the boy

for a number of years had shown neither growth nor sexual development, then suddenly achieved both within a comparatively short period.

Wallen-Lawrence (personal communication) does not believe the 30 cc. of Phyone consumed by this patient was sufficient with its small trace of gonad-stimulating hormone, to produce the gonad-stimulating effect obtained in the present case. She is rather inclined to believe that the latter was a good deed of nature.

## SUMMARY

A case is presented of a 16-year-old boy of the Levi-Lorain type of pituitary infantilism. In addition to stunted growth and sexual infantilism, he presented a delay in the closure of certain of his epiphyses. After a period devoid of physical advancement for a number of years, treatment with commercial growth-stimulating pituitary preparations (Antuitrin and later Phyone) was carried out for several months. On 43 injections of Antuitrin, the patient gained 1 inch, and on the Phyone, 2¼ inches, a total of 3¼ inches gained in 18 months. His weight increased 11½ pounds in the same period. The genital hypoplasia was corrected with satisfactory development of the testes, penis, and pubic hair and an increase in libido. His mental attitude was completely changed.

# AN EVALUATION OF PERIODICAL LITERATURE FROM THE STANDPOINT OF ENDOCRINOLOGY

JENNIE GREGORY, M.S.
BOSTON

In a recent issue of this Journal Mengart published an appraisal of medical and biochemical periodicals from the standpoint of their usefulness to the research worker in the endocrinology of sex. He based his study on the references included in Allen's "Sex and Internal Secretions." The present survey enlarges the field to include all phases of endocrinology. The data presented herein augment those of Mengert and add weight to his findings.

A number of bibliographies I compiled during the year were studied by tabulating the number of references for every journal cited twice or oftener. The percentage of references per journal and cumulative percentages were then computed. The subjects of these bibliographies and the source and number of references in each are given below.

| | | |
|---|---|---|
| A. | Interrelationship of the Endocrine Glands from Index Medicus, 1933-1927 | 75 references |
| B. | Adrenal Cortex Preparations from Chemical Abstracts, 1933-1924; from Index Medicus, 1933-1927 | 97 references |
| C. | Kidney Extracts, from Index Medicus, 1933-1900 | 64 references |
| D. | Corpus Luteum, from Index Medicus, 1933-1927 | 189 references |
| E. | Diuresis and Diuretics (hormonal influence on), from Index Medicus, 1933-1927 | 333 references |
| F. | Thyroid, from Index Medicus, 1930-1934; from Chemical Abstracts, 1933-1934 | 282 references |
| | Total number of references | 1040 |

A second tabulation was made in the same manner as the first but using the references given by A. T. Cameron in his "Recent Advances in Endocrinology" (Blakiston, 1934). The results of these two tabulations were then compared with results obtained by Mengert, Sherwood, and Jenkins (1, 2, 3). Mengert's study furnished him with 2474 references from 335 periodicals. Sherwood's data were based on references appearing in the Journal of the American Medical Association since 1925 and

included 4912 references from 556 periodicals, while Jenkin's data were based on references given in the Journal of the American Medical Association, the British Medical Journal, and the Klinische Wochenschrift.

The result of this tabulation of my references and Mengert's references was three lists of journals in the order of the number of times cited. Figure 1 is a composite of these and was obtained by adding the percentages of each journal from each of the three lists and then rearranging in order of importance, discarding all but the first 25. This list represents 4190 references from 504 journals.

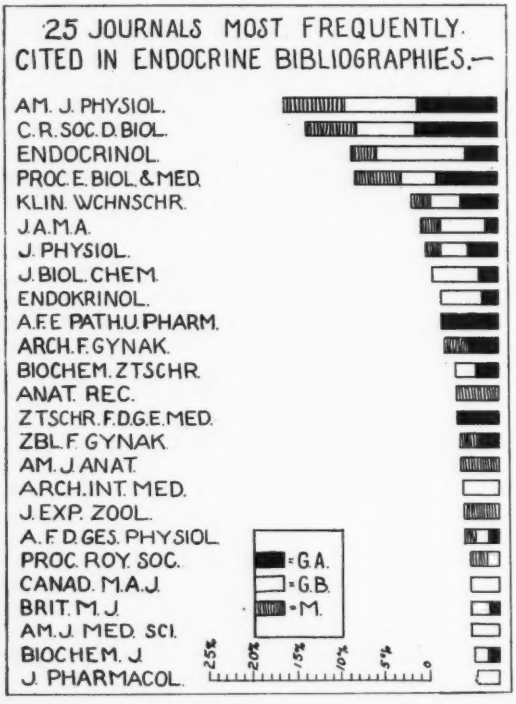



**Figure I.** This list was obtained by adding the percentages of citation for each journal from Mengert's data (M) and my data (G. A.—my bibliographies; G. B.—Cameron's bibliographies), rearranging in order of importance and discarding all but the first twenty-five.

The final tables indicate what percentage of the journals must be read in order to cover the endocrine literature adequately. From Table I it is apparent that the endocrinologist who reads only the first three journals will cover a fourth of the literature pertaining to his field. Jenkins and Sherwood likewise found that in the field of general medicine three journals encompassed a fourth of the pertinent literature. The reader who is to cover half the field must read ten journals, and if he wishes to cover two-thirds or more he must read seventeen or more journals.

TABLE I

PERCENTAGE OF REFERENCES IN VARIOUS NUMBERS OF PERIODICALS. COMPARISON OF GREGORY, MENGERT, JENKINS AND SHERWOOD

| | Percentage of Articles in First | | | | | |
|---|---|---|---|---|---|---|
| | 3 | 5 | 10 | 17 | 30 | 50 |
| General Endocrinology— | | | | | | |
| Gregory A | 25% | 36% | 50% | 63% | 75% | .... |
| A1 | 25% | 35% | 55% | 71% | 84% | 94% |
| Endocrinology of Sex— | | | | | | |
| Mengert | .... | 26% | .... | 50% | .... | .... |
| General Literature of Medicine— | | | | | | |
| Jenkins | 25% | .... | .... | 50% | .... | .... |
| Sherwood | .... | .... | 38% | .... | .... | 70% |

TABLE II

PERCENTAGE OF REFERENCES IN PERCENTAGE OF JOURNALS

| | Percentage of References in Percentage of Journals | | |
|---|---|---|---|
| | 25% in | 50% in | 75% in |
| General Endocrinology— | | | |
| Gregory A | 3.3% | 10.1% | 30.2% |
| A1 | 4.3% | 12.9% | 28.5% |
| Endocrinology of Sex— | | | |
| Mengert | 1.2% | 4.7% | ..... |

CONCLUSIONS

1. Twenty-five per cent of the articles in the field of endocrinology appear in three journals—American Journal of Physiology, Comptes rendus des Séances de la Société de biologie, and Endocrinology. The fourth journal in importance is Proceedings of Society for Experimental Biology and Medicine.

2. From fifty to seventy per cent of the articles appear in approximately twenty journals.

3. From seventy to ninety-four per cent of the articles appear in approximately fifty journals.

4. Seventy-five per cent of the material should be found in the periodicals listed in Figure 1. This list should serve as a useful guide to research workers in the field of endocrinology.

REFERENCES

1. Mengert: Endocrinology, **18**: 421. 1934.
2. Sherwood: Northwest. Med. **31**: 273. 1932.
3. Jenkins: J. A. M. A. **97**: 608. 1931.

# Book Reviews

RECENT ADVANCES IN ENDOCRINOLOGY. A. T. Cameron. P. Blakiston's Son & Co., Inc., Philadelphia. 1934.

In the compilation of a book of the type offered much depends upon the interpretation of the word "recent." If narrowly defined, older work is excluded and the text would be intelligible only to specialized students of the subject. The author has defined it broadly and has permitted himself to include a considerable amount of standard textbook material by way of rendering intelligible the strictly recent advances. By so doing he has, of course, restricted the space available for actual recent contributions.

In such an undertaking it is necessary to make arbitrary choice among the hundreds of annual contributions. As to which will ultimately prove of greatest significance considerable leeway of judgment is offered. On the whole the selections made have been judicious. The result is a readable and intelligible book which gives a very fair picture of endocrinology as it existed a few months ago. For obvious reasons the latest work can never be found in a book of this type.

The work will be regarded most highly among endocrinologists for its authoritative discussion of the chemical phases of endocrinology. The treatment of the sex hormones is especially noteworthy in this regard.

The book is a valuable working tool for the endocrine specialist and is well worth the attention of the practicing physician.

PRACTICAL ENDOCRINOLOGY. Max A. Goldzieher. D. Appleton-Century Company, New York and London. 1935. Pp. 326.

So rapid has been the advancement of endocrinology over recent years that none but the specialists can hope to maintain any adequate command of the literature. Nevertheless the alert practitioner of medicine recognizes the frequency with which endocrine problems are presented in his daily practice. There is accordingly a genuine need for an up-to-date book on practical endocrinology in the best sense of that term. Several authors in recent years have essayed the difficult task of writing such a book but in general they have attained simplicity by gross omissions or by overfacile generalizations which contain more than a little of the mendacity of partial statement.

Goldzieher has skillfully avoided these two pitfalls. Condensation has been attained by fixing attention upon those parts of the subject matter that can now be related directly to the practice of medicine. The fact is recognized that upon certain points honest differences of opinion of competent endocrinologists exist. The author has taken the responsibility of stating his opinions in dogmatic form, leaving it to the reader to decide whether he shall follow a single guide with the possibility of being led occasionally into error or whether he shall read further and weigh the evidence upon controversial points for himself. This treatment necessarily raises the question of the competence of the author. The reviewer has detected few instances in which the method has led to dubious statements. The author has brought to bear many years of experience both in labora-

tory studies—particularly pathological—and in clinical treatment of patients.

Especially authoritative is the treatment of the adrenal glands as factors in obesity and of the therapeutics of pituitary cachexia, the author's recent work on the specific dynamic action test and the fat meal test for pituitary deficiency.

The only serious criticism to be made of the work is in the choice of illustrations. The photographs that are reproduced are in some instances "fuzzy" and one at least showing the effect of treatment in hypopituitary obesity is definitely misleading. On page 51 is also a textual statement that is of dubious validity in that a rest period of "at least ten minutes" is recommended in the basal metabolism test. It is doubtful if a rest period of this length is ever adequate.

Altogether, considering the numerous difficulties that beset the writing of such a work the author has been eminently successful and the book can be heartily recommended to the class of readers for whom it is intended.

ÜBER WACHSTUM UND RUCKGANG, UBER STANDARDISIERUNG, INDIVIDUALISIERUNG UND BAULICHE INVIDUALTYPEN IM LAUFE DES NORMALEN POSTFOTALLEBENS. Konstitutionsanatomische Studien an Kaninchen. Hammar, J. Aug., IV—539 pp. Akademische Verlagsgesellschaft, Leipzig. 1932. (Reprint from Ztschr. f. mikr.-anat. Forsch. **29**: 1-540. 1932.)

This book is divided into five parts, viz.: general viewpoint and methods, weights of the body and its individual organs, average increase and decrease of the body and its individual parts during the life span, variation and correlation of the body and its organs, and total body builds.

Healthy rabbits from new-born to 42 months old were used. Skeleton, fat, lymphoid tissue, kidney and liver, and the principal endocrine organs were dissected and weighed. Larger parts or organs were weighed directly; smaller organs or parts were fixed, cut in serial sections of known thickness and drawn to an enlarged scale. The paper drawings were then weighed and the weights equated back to the original. Parts of organs, e.g., colloid and parenchyma of thyroid, were correlated with each other, and also whole organs or systems against each other and against body weight.

Increase or decrease in parts of the body is discussed in detail in the second part. Age periods used are pre-pubertal, pubertal, and post-pubertal. In the pre-pubertal period, fat animals were more advanced than thin animals of a corresponding age. Fat was closely correlated with the lymphoid tissue, the seminiferous tubules, and the musculature. Musculature and fat were correlated throughout life. Sexual maturity in both sexes was correlated with a slight increase in compact parenchyma and with new formations of colloid in the thyroid. The thymus showed no marked correlations with any other organs. The rule that old age was marked by organ regression did not hold. Adrenal medulla, parathyroid III, anterior and posterior lobes of hypophysis continued to grow after the twelfth month.

Variation of each of the organs or parts was studied. Endocrine organs most variable in the pubertal period were also most variable in the post-pubertal. Correlations were determined for each of the organs and parts with each of the other organs or parts and with the body as a whole. Individual differences in addition to age differences were very apparent in the endocrine system.

After exhaustive analysis of the different types of individual organs and parts, Hammar analyzes different builds of the whole body. As a rule a large exterior, i.e., large skeleton, heavy muscle and fat, is correlated with large internal organs. Body builds are divided into (1) thymo-lymphatic types, i.e., body builds associated with certain types of lymphoid tissues; (2) first endocrine type, correlated, among other things, with compact thyroid parenchyma, parathyroids, anterior lobe of hypophysis, and adrenal cortex; (3) second endocrine type, correlated with colloid of the thyroid, intermediate lobe of hypophysis, and adrenal medulla. Partial castrate males showed a eunuchoid body build thus demonstrating the influence of gonads on body proportions.

The book closes with a short chapter on the life history of rabbits in which the age changes of the body as a whole and of the different organs are summarized. This monograph represents an elaborate study of constitution and reflects well the author's idea of how studies of this type ought to be carried out. It should serve as an example of the application of the more exact methods that modern conditions demand, and is one more monument by which the long scientific career of J. August Hammar will be remembered.

HUMAN STERILITY. CAUSATION, DIAGNOSIS AND TREATMENT. A PRACTICAL MANUAL OF CLINIC PROCEDURE. Samuel Raynor Meaker. Pp. 276, The Williams & Wilkins Company, Baltimore. 1934.

The book is issued under the auspices of the National Committee on Maternal Health. The announced objective is "to assemble completely knowledge now established, discounting the traditional fallacies and including all the modern discoveries." The presentation is qualified by the author's declared belief that "only in the last twenty years has any significant progress been made in the diagnosis and treatment of human sterility. Within that period the advance has been great. Clinical management, when it has the advantage of the newer knowledge, is now far more efficient—a fact that has caused a wave of new interest in the subject." Although the literature has been to some extent considered the book is largely based upon the experience of the author himself and of his colleagues who cooperated in a joint study of sterility.

Only an extensive review could do justice to the many excellencies of the book—point out the ways in which it is of value to the practicing clinician and of interest to the endocrine specialist who is concerned with the application of the newer knowledge to practical medicine.

Infertility is almost always a relative term. The given subject may present any picture ranging from substantially 100 per cent fertility to absolute sterility. Special stress is laid upon the fact that individual fertility or infertility and that of a given mating are by no means synonymous. Relatively low fertility in both mates may result in an infertile marriage though both partners are individually of fair fertility and either may become a parent in other matings. Ordinarily infertility is proved to be the result not of one but often of several individual contributing causes. In the infertile matings that were studied an average of between four and five individual contributing causes was noted. The husbands were predominantly at fault in one-third and the wives in two-thirds of the cases.

The general plan of the work can be indicated by topics treated. These include "Requisites of Fertility," "Nature of Causative Factors," "Incidence and Distribution of Causative Factors." Then follows a section on general principles of investigation indicating the functions of various collaborators and a schedule of activities running through eight days. Metabolic and clinical studies run concurrently. While the wife is receiving preliminary gynecologic and anamnestic examination the husband fares similarly at the hands of a genitourologist. At the same time urine samples are being analyzed and basal metabolism determinations and other vital function tests are begun. The last portion of the schedule is devoted to post-coital studies of husband and wife and completion of laboratory investigations. Subsequent consultation of specialists is utilized as need is discovered. The details of gynecologic and urologic investigations are set forth at length. This section of the book is eminently practical in the best sense of that term.

Readers of this Journal will be most interested in the topic of endocrinologic investigations. This section embodies the most readable presentation of the well-known work of the Evans Memorial that has been offered. This Institution, under the direction of the late Dr. A. W. Rowe, who contributed the text of this section, has extended over a period of twenty years. The intent has been to develop a method of endocrine diagnosis "based upon objective standards." The general project included three successive phases. "The first phase involved carrying out on some hundreds of individuals the elaborate investigation described in this and in the following chapter, together with numerous other tests which were ultimately discarded as being of less practical value. Thus normal standards were established." "In the second phase a similar study was conducted on several distinct groups of patients who exhibited unquestionable endocrine hypofunction, in most instances as a result of the surgical ablation of some major gland. Gradually it became possible to recognize, not single findings, but patterns running through the whole series of tests, characteristic, respectively, of the pituitary, thyroid, and ovarian disorders." From the standpoint of technical physiology as well as of endocrinology as a specialty it is to be regretted that the author had not yet published this control and paradigmatic material in detail. "The third phase of the work, which is going on at present, is the application of these methods to cases of unknown character for the purpose of diagnosis."

The first chapter of the section presents an interesting allocation of such things as weight abnormality, skin diseases, abnormalities of hair, headache, vertigo, fatigability, etc., to the various endocrine categories. The next chapter presents a valuable epitome of endocrinologic investigative methods, including physical examination, metabolic determinations, urine examination, blood examination and various special examinations. The next chapter discusses the methods of combining results of these various studies to reach a diagnosis. From any point of view little but praise can be offered regarding this chapter.

The book concludes with a final section on prognosis, treatment, and results of treatment. As an indication of the potentialities of adequate treatment the results are reported in thirty-four cases of sterility investigated and treated by the author by the methods recommended and subsequently "followed up." In precisely half the cases pregnancy resulted and in 15 instances the pregnancy resulted in a living baby. In view of the fact that these were for the most part stubborn cases in which the subjects had already experienced unsuccessful treatment the results are

strikingly encouraging. What part the various therapeutic procedures individually played in the results is not stated.

Should the book secure the wide circle of readers which its intrinsic merit warrants it will no doubt prove to be an important social document. Acquaintance with its contents will unquestionably add materially to success in the treatment of human infertility.

# Abstract Department

**Diabetes mellitus in association with degeneration of the suprarenal glands.** Brookfield, R. W. and H. V. Corbett, Brit. M. J. **1**: 231. 1934.

The association of diabetes mellitus with gross pathological changes in the suprarenal glands is uncommon. The authors have therefore reported the case of a woman of 61 years whose blood sugar on admission was 1040 mg. per cent. Despite the administration of large doses of insulin (460 units the first 24 hours, 240 units daily for 3 days, and thereafter 160 units daily), death supervened 10 days later. Necropsy revealed the presence of bilateral cystic suprarenal glands. Microscopically the cortex showed marked changes involving particularly the fasciculate and reticulate layers. In addition there was some fibrosis and much round-celled infiltration. No normal medullary tissue was found. Despite the existence of advanced disease of the suprarenal capsules the classical symptoms of Addison's disease were not observed.

—H. C. Shepardson.

**Influence of adreno-cortical extract and of glucose on muscle glycogen recovery in adrenalectomized animals (Influencia del extracto cortico-suprarrenal y de la glucosa sobre la recomposición del glucógeno muscular en los suprarrenoprivos).** Dambrosi, R., L. F. Leloir and A. Novelli, Rev. Soc. argent. de biol. **9**: 417. 1933.

Adrenalectomized dogs operated upon 24-48 hours previously, received 1 gram glucose per kg. intravenously after the leg muscles were tetanized for 15 minutes. Glycemia was high, but muscle glycogen recovery after fatigue was definitely below normal and comparable to that seen in adrenalectomized animals which had not received glucose. Only in one experiment of 5 was there a normal recovery. Swingle and Pfiffner's extract was injected into adrenalectomized dogs (15-20 cc. intraperitoneally) in doses of 5 cc. the last two hours before fatigue. Muscle glycogen was restored in quantities well above normal. The extract did not influence the muscle glycogen recovery of normal animals in the doses used.—J. T. L.

**The effect of diverting the adrenal vein blood into the portal vein on the blood sugar of dogs.** Dragstedt, L. R., Am. J. Physiol. **108**: 42. 1934.

A method for producing a permanent diversion of adrenal vein blood into the portal vein in dogs has been described. Such a diversion was found in 4 dogs to cause a moderate persistent elevation and instability in the level of the blood sugar. Glycosuria was not produced and no increased tolerance to insulin was observed.—Author's Summary.

**Pheochromocytoma of the suprarenal medulla (paraganglioma); a clinicopathologic study.** Eisenberg, A. A. and H. Wallerstein, Arch. Path. **14**: 818. 1932. Abst., Arch. Neurol. & Psychiat. **30**: 916.

The purposes in this article are: to collect all the recorded cases of pheochromocytoma of the suprarenal gland; to present the salient clinical and pathologic features of all these cases, and to attempt to reduce them to a common denominator, i.e., to present their clinicopathologic cross-section, and to report the fifth case of malignant pheochromocytoma of the suprarenal gland, one that is associated with another primary malignant growth (of the thyroid gland) and an unusual blood picture. Fifty-three cases of pheochromocytoma of the medulla of the suprarenal gland collected from the literature are tabulated with their main clinical and pathologic features. A new case of malignant pheochromocytoma of the medulla of the suprarenal gland is presented, with the following unusual features: (a) coexistence of another primary malignant neoplasm (of the thyroid gland), (b) widespread metastases from the pheochromocytoma, with none from the carcinoma of the thyroid gland, and (c) a very unusual blood picture. Only 5 of the 53 cases previously reported were malignant, but all of them showed widespread metastasis. Association of benign pheochromocytoma with other tumors is not rare, several cases having been reported of its association with multiple neurofibromas, with adenomas (of the thyroid gland, liver and pancreas) and with hypernephromas.

In only the one case was a malignant pheochromocytoma associated with another primary malignant tumor. All known cases of malignant suprarenal pheochromocytoma were bilateral. The incidence of the tumor is about even as to sex; it is greatest on the right side and in patients in the fifth decade of life. The most striking histologic features are: the greatest imaginable irregularity in the size and shape of the cells and of the nuclei, the reaction to the chromaffin and the rich vasculature. The most interesting feature is the relation of these tumors to hypertension. About one-half of all the patients showed hypertension, some with atherosclerosis and others without it. While in some cases of tumor of the suprarenal cortex hypertension was continuous, in a large majority of the cases of tumors of the suprarenal medulla in which it was present it was of paroxysmal type—but only in the cases in which the tumor was benign, as all patients with malignant medullary tumor showed either no hypertension at all or hypotension. The attempts to correlate hyperplasia of chromaffin tissue with hypertension are not successful because of the absence of proof that hypersuprarenalemia exists in such cases, and also because it is not at all established that hypersuprarenalemia is responsible for hypertension.

**Adreno-genital syndrome; illustrative case, with especial reference to its relation to Cushing's new pituitary syndrome.** Foggie, W. E. and G. L. Montgomery, Edinburgh M. J. **41**: 29. 1934. Abst., J. A. M. A. **102**: 1442.

The authors report the case of a woman of 36 who became gradually changed in both physical and mental characteristics after the birth of a stillborn child. Adiposity, hirsuties and amenorrhea with added pigmentation became evident. Further, there was a change in her voice. At first there was an overactivity of body and mind with special mental and psychosexual phenomena, but later there was a physical wasting with marked mental degeneration before complete dissolution set in. The whole process lasted two and a half years. Pathologically there was bilateral hyperplasia in the cortices of the suprarenals with some adenomatous formations. There was also advanced renal sclerosis of vascular origin. The clinical picture represented the assemblage of symptoms that directs attention to the suprarenal. Apart from the underlying cause this patient exhibited what is recognized as the corticogenital or suprareno-genital syndrome. Cook was one of the first to associate such a condition with a lesion of the suprarenal cortex, while Apert and Gallais did much to help in the elucidation of the clinical side. It is now recognized that there are various types of this condition: embryonic, with resulting hermaphroditism; early life, with precocity, exaggerated muscularity and secondary sex characteristics; puberty and after, with adiposity and secondary sex phenomena, occurring especially in women and associated with the reproductive period of life, and postmenstrual type, with less marked changes. The present case belongs to the third group and is marked by all the signs and symptoms usually associated with it. The three cardinal signs are amenorrhea or better, sexual dystrophy, as men may be affected, hypertrichosis and adiposity. In the present case menstruation was irregular at first, but there was amenorrhea for the last six months of the patient's life. The pathologic evidence was not considered conclusive, as the suprarenal lesion did not appear to be sufficient to account for the gross changes that occurred and the case had obviously many points of resemblance with the basophilic type described by Cushing, but in the absence of a report on the hypophysis one can only leave the final diagnosis an open one. Such a case with pluriglandular suggestion would be unlikely to benefit by operative treatment directed to the suprarenal. If Cushing is right in his generalization, the logical thing would be to concentrate on the hypophysis either by operation or by roentgen therapy. In some cases of suprarenal tumors of local origin, roentgen therapy has been reported as beneficial.

**The anatomical and functional disturbances of the adrenal gland in general visceroptosis.** Fowler, O. S., J. of Urol. **31**: 363. 1934.

In 75 autopsies on unselected cases, the supports of the kidney and adrenal were examined and the relation of the latter to visceroptosis studied. The adrenal was dragged down to a greater or lesser degree in this condition and some of the symptoms of visceroptosis could be explained as due to interference with adrenal function. Any type of nephropexy must take the proper support of the adrenal into consideration. If it does, this type of operation may be expected to be of marked benefit.—J. C. D.

**The effect of diet, insulin and thyroxine upon the adrenaline content of the suprarenal glands.** Gohar, H. A. F., J. Physiol. **80:** 305. 1933. Abst., Physiol. Absts. **19:** 49.

With high protein diet there is no marked effect upon the adrenal gland (rat), but fat diet leads to a diminution of the absolute content of adrenaline and of the total weight of the glands; the relative amount of adrenaline per gram of gland is also slightly diminished. Carbohydrate diet also leads to a diminution of the absolute content of adrenaline, and since the weight of the gland is strikingly diminished, the relative amount of adrenaline per gram of gland is considerably increased. Repeated administration of insulin in subconvulsive doses leads to an increase in the weight of the glands and of their adrenaline content. In convulsive doses insulin leads to a depletion of the adrenaline store; this effect of insulin is produced through the nervous system as well as by peripheral action on the glands. Repeated injection of thyroxine also leads to an increase in weight of the gland and of adrenaline content.

**The extraction of the adrenal cortical hormone from the interrenal body of fishes.** Grollman, A., W. M. Firor and E. Grollman, Am. J. Physiol. **108:** 237. 1934.

An extract was made of the interrenal bodies of skates. The Grollman-Firor method was used. Adrenalectomized young rats (number not stated) to which the extract was administered outgrew their controls.—R. G. H.

**Adrenaline content of the adrenals in hypophysectomized animals (El contenido de las suprarrenales de los hipofisoprivos en adrenalina).** Houssay, B. A. and P. Mazzocco, Rev. Soc. argent. de biol. **9:** 220. 1933.

In dogs (6 hypophysectomized, 4 with lesions in the tuber cinereum and 10 controls) the adrenaline content of the adrenals was determined by the Cannon, Folin and Denis method. After hypophysectomy the percentage content increased, due to cortical atrophy. The total content was normal or slightly below normal. In hypophysectomized toads (batches of 5) the total adrenaline content of the adrenals (1, 2, 3, 4 and 7 weeks after operation) was normal.—J. T. L.

**Action of anterior pituitary extract on adrenal glands (Accion del extracto antero-hipofisario sobre las glandulas adrenales).** Houssay, B. A., A. Biasotti, P. Mazzocco and R. Sammartino, Rev. Soc. argent. de biol. **9:** 262. 1933.

Intraperitoneal injection of anterior lobe extract (alkaline) into dogs produced an enlargement of the adrenals with an increase in weight. At first there was an absolute and relative decrease in the adrenaline content, later only a relative decrease. The cortical cells had less numerous and small fatty inclusions, in parts they were very scarce or completely missing. This hypertrophy is still observed after hypophysectomy, castration, thyroidectomy and section of the splanchnics and lumbar sympathetic.—J. T. L.

**Epinephrine secretions in insulin hypoglycemia and in Pal's vascular crises (Zur Frage der Adrenalinausschüttung bei der Insulinhypoglykämie und bei Pal'schen Gefässkrisen).** Kugelmann, B., Klin. Wchnschr. **12:** 1488. 1933. Abst., J. A. M. A. **101:** 1839.

The author gained the impression that the hypoglycemic symptoms, palpitation of the heart, tremor, pallor and feeling of pressure over the sternum, are not the direct result of the action of insulin but are caused by an increased secretion of epinephrine. He reasoned that if this theory was correct it should be possible to produce by the simultaneous administration of ergotamine tartrate and insulin a hypoglycemic condition in which the epinephrine symptoms would be absent, as it is known that ergotamine tartrate checks the effects of epinephrine. By the simultaneous administration of insulin and ergotamine tartrate he succeeded in producing in 4 of 10 patients a hypoglycemic condition in which involvement of the vascular and circulatory apparatus was absent. This proves that the hypoglycemic condition consists of two components, a direct insulin action and a regulatory epinephrine action. In Pal's vascular crises, during increase of blood pressure the author observed hyperglycemia, hyperleukocytosis and lymphocytosis, conditions that can be explained by an endogenic epinephrine elimination.

**Luteinizing hormone in suprarenal cortex (Sur la présence de l'hormone lutéinisante dans l'écorce surrénale).** Migliavacca, A., Arch. internat. de physiol. **36:** 137. 1933. Abst., Physiol. Absts. **18:** 652.

Injection of suprarenal cortical extract causes precocious maturation of the genital organs in white mice, the results being similar to those caused by anterior pituitary hormone. In guinea-pigs whose pituitaries had been destroyed by x-rays, administration of this suprarenal cortical extract produced in immature animals a luteinization of the peripheral connective tissue elements of atresic follicles; in adult animals the formation of luteal tissue was more marked and more widespread. These results confirm the relationship between the suprarenal cortex and the genital organs.

**The effect of fluid deprivation and fluid intake upon the revival of dogs from adrenal insufficiency.** Swingle, W. W., J. J. Pfiffner, H. M. Vars and W. M. Parkins, Am. J. Physiol. **108:** 144. 1934.

Eight animals were used in the experiments with similar results in all cases. Adrenalectomized dogs, exhibiting severe symptoms and deprived of food and water for periods varying from 24 to 72 hours while receiving extract, are capable of mobilizing sufficient fluid (and salt presumably) in the tissues and interstitial spaces for transfer to the blood stream to permit revival of the animal to the point where to all appearances, and in so far as activity, appetite and vigor are concerned the dog appears and acts normal. The blood pressure, hemoglobin and urea nitrogen do not, however, attain their normal levels. Animals presenting severe symptoms and verging on prostration can be restored to apparently normal health by injection of cortical hormone without food (or salt) intake, but some fluid is required for complete restoration of the blood pressure, hemoglobin and urea nitrogen to normal levels. The adrenalectomized dog in the absence of the cortical hormone is apparently unable to mobilize the fluid of its tissues and interstitial tissue spaces for use in maintaining a normal volume of circulating fluid. Hypoglycemia cannot be regarded as an important factor in these experiments, since significant alterations of the blood glucose were not observed in this series of experimental animals, even when they exhibited severe symptoms.—Authors' Summary.

**The effect of sodium chloride administration upon adrenalectomized dogs not receiving extract.** Swingle, W. W., J. J. Pfiffner, H. M. Vars and W. M. Parkins, Am. J. Physiol. **108:** 159. 1934.

Feeding sodium chloride to the point of tolerance to bilaterally adrenalectomized dogs not receiving cortical extract prolongs somewhat the interval intervening between cessation of extract injections and development of adrenal insufficiency. Seven animals were used in the experiments. Three animals remained free from symptoms for 14 days, one for 12 days, one 21 days, one 19 days, and one 50 days. Salt was withdrawn from the diet of the long surviving animal on the 50th day. Four days later the dog exhibited severe symptoms of insufficiency. Sodium chloride and water cannot be regarded as an effective substitute for the cortical hormone in the bilaterally adrenalectomized dog since it was necessary to inject cortical extract in order to save the animals when they sooner or later developed severe symptoms. A decline in the level of blood glucose is likely to develop in the adrenalectomized dog fed sodium chloride to the point of tolerance. Dogs on ordinary diets when permitted to develop severe symptoms of insufficiency by withdrawal of extract rarely show changes in the blood sugar. Intraperitoneal injections of large quantities of 0.85 or 0.9% saline were ineffective in relieving the symptoms of severe insufficiency. Such injections proved effective in relieving gross symptoms in 2 animals exhibiting mild insufficiency; the blood pressure, blood urea nitrogen, and hemoglobin were restored to their normal levels by such treatment.—Authors' Summary.

**The effects of pregnancy on the organ weights of the albino rat.** Abramson, M., Am. J. Obst. & Gynec. **27:** 492. 1934.

Data were obtained on 66 animals in three groups: 22 controls, 22 in the first half of pregnancy and 22 in the second half of pregnancy. In addition to numerous other features, the weights of several endocrine glands were compared in the three groups. The data were subjected to statistical analysis. The weight of the hypophysis was not significantly affected. That of the thy-

roid, thymus and ovaries was significantly decreased during pregnancy. The weight of the ovaries remained normal during the first half and showed a slight increase in the latter half of pregnancy.—R. G. H.

**Chemical transmitter of vagus effects to the stomach.** Dale, H. H. and W. Feldberg, J. Physiol. **81:** 320. 1934.

Venous blood derived from the stomach of chloralosed dogs (intestine extirpated) gave negative tests for acetylcholine. However, after administration of eserine to suppress the action of cholinesterase, the venous blood tested on leech muscle, the frog's heart or the blood pressure of cats gave indications of acetylcholine in concentrations of approximately $1:500 \times 10^6$. Associated with augmented gastric motility produced by stimulation of the peripheral end of the thoracic vagi (in the eserinized animal) acetylcholine concentration increased up to fourfold. Perfusion of the gastric blood vessels with Locke's solution containing eserine lead to similar results both before and after vagus stimulation. The evidence, according to the authors, indicates that stimulation of the gastric vagus leads to chemical transmission of vagal effects through a liberation of acetylcholine probably both at the ganglia and at the nerve-muscle junction.—J. P. Quigley.

**Relation of thyroid, adrenals and islands of Langerhans to malacic diseases of bone.** Golden, R. and H. Abbott, Am. J. Roentgenol. **30:** 641. 1933. Abst., J. A. M. A. **102:** 874.

The authors examined the roentgenograms in 110 cases of hyperthyroidism, 51 of hypothyroidism and 14 of Addison's disease, and 60 roentgenograms of adult diabetic patients. They conclude that hyperthyroidism produces an abnormal elimination of calcium, the mechanism of which is not understood. It seems to be frequently associated with a decalcification of the bones demonstrable on the roentgenogram by suitable comparison with the normal, which is so slight as to be of little, if any, importance. In rare cases the decalcification of the bones may be extreme. Its appearance, however, is not characteristic of thyrotoxicosis. In cretinism and infantile myxedema there is a widening of the cortex of the long bones without loss of calcium. Hypothyroidism in adults is apparently associated with no greater incidence of decalcification of bones than that which might be encountered in any group of patients of the same age. Although suprarenal secretion directly or indirectly influences calcium metabolism and although the suprarenals may be indirectly involved in a pluriglandular imbalance in certain cases of osteomalacia, the evidence does not seem to justify the assumption that decalcification of the bones results directly from disease of the suprarenals or dysfunction. Calcium metabolism is intimately linked with carbohydrate metabolism. The available evidence indicates that a calcium loss may take place in diabetes, especially with acidosis. In children the disease may be associated with a decrease in the density of the bones on the roentgenogram, which in one case was so marked as to suggest osteomalacia. The question may be raised as to how much of this is of endocrine and how much of nutritional origin. Roentgen evidence of definite important skeletal decalcification in diabetic adults which can be attributed directly to the disease is lacking.

**Growth and development in its relation to children and orthodontic problems.** Spinney, H. L., Internat. J. Orthodontia, **20:** 604. 1934.

A study of endocrinology and of metabolism in relation to orthodontia leads the author to the conclusion that the dental practitioner meets three types of tooth malformation. (1) There is a group of patients in whom there is slow response of the osseous structures to mechanical stimulation, delayed eruption of the permanent teeth, delayed exfoliation of the deciduous teeth, lack of density of the crowns, progressive decay and slow repair. Usually the patients show retarded physical growth and development with various associated symptoms indicating inactivity of the thyroid and pituitary. (2) There is a group in which the teeth are large, well-shaped, with more than normal spacing and in which the osseous structure is hyperplastic due to rapid growth and low mineral content. The teeth are very susceptible to local influence and give rapid response to mechanical stimulation. The dentist has difficulty in fixating the teeth, however, after he has them in alignment. Calcium and light therapy is valuable in this group. The underlying endocrine condition seems to be hyperfunctioning of the pituitary with lack of thyroid stimulation.

(3) There is a group believed to be entirely congenital marked by overgrowth of the skeletal structure and clinical symptoms of thyroid and pituitary overactivity during the early years. This is followed by relative inactivity of the thyroid, causing irregularities in the growth processes.—R. G. H.

**The cause of the onset of labor; a hormonal investigation.** Witherspoon, J. T., Am. J. Obst. & Gynec. **27**: 559. 1934.

The author reports briefly on the results of a study designed to determine the efficacy of various endocrine products in the induction of labor. The substances used were theelin, follicular fluid, amniotin, progynon and parturient blood. In 11 instances delivery occurred within 36 hours of the injection, but in 34 instances failure resulted. In conclusion the author comments upon the current profound ignorance of the causation of labor. He urges the desirability of further studies on this topic.—R. G. H.

**Ovarian therapy; relationship of the female sex hormone to hemophilia.** Brem, J. and J. S. Leopold, J. A. M. A. **102**: 200. 1934.

Following reports of the value of ovarian therapy in and the intimate relationship of the female sex hormone to hemophilia, the problem was investigated from three different angles. Parenteral injection of whole ovarian extract and ovarian follicular hormone were given to a 9½-year-old hemophiliac patient, and the effect on his general condition was noted. Coincidentally the coagulation time of the blood was determined at regular intervals to check the clinical course. The urines of two hemophiliac patients and normal male controls were assayed for the presence of the female sex hormone or estrogenic substance to determine the relationship of the female sex hormone to hemophilia. After the parenteral injection of the ovarian follicular hormone, an attempt was made to recover it from the urine of one hemophiliac patient. The results obtained showed that neither whole ovarian extract nor ovarian follicular hormone had any significant effect in reducing the coagulation time of the blood nor did these hormones prevent epistaxis, subcutaneous hemorrhages, and hemarthrosis. The presence of the female sex hormone in the urine of two hemophiliac brothers was not demonstrated; neither was it found in the urines of four normal male controls. The estrogenic substance of known potency, which was used by us, was not recoverable in the urine after parenteral injection. Because of the reports of reduction in growth and atrophy of sexual organs in young rats after prolonged administration of the estrogenic substance and because pure synthetic compounds of known molecular struction can possess both estrogenic and carcinogenic properties, a warning against the indiscriminate use of the ovarian follicular hormone in hemophilia is sounded.—J. Brem.

**Effect of vasectomy on the testis in rats and rabbits (Influence de la vasectomie sur le testicule du rat et du lapin).** Brouha, L. and L. Desclin. Compt. rend. Soc. de biol. **113**: 83. 1933.

Section of the vas failed to produce, after 4 to 7 months in rats and after 13 months in rabbits, any marked histological change in either the cells of the tubules or the interstitial tissue.—J. C. D.

**A new method for the prediction of the sex of the fetus.** Davis, M., New England J. Med. **210**: 421. 1934.

At attempt has been made to discover a simple and accurate test for the prediction of the sex of the fetus. The method consists in the intradermal injection of 0.1 to 0.2 cc. of the testicular extract. As a result of this injection, a variety of reactions takes place which have been arbitrarily labeled as negative (no reaction), one plus (a red area from 12 mm. in diameter), two plus (a red area from 12 to 20 mm. in diameter) and three plus (a red area more than 20 mm. in diameter). The readings were made from five to ten minutes after injection, and the reaction disappeared within a few hours. A negative reaction indicated a female fetus, the two and three plus reactions showed male children. The records of the one plus reaction were almost equally divided between the males and the females. A total of 534 cases were tested; of these, 66 gave one plus reactions; 156 of 174 females were predicted correctly, an accuracy of 89.6%, and 242 of 294 males were prognosticated correctly, an accuracy of 82.3%. The exact mechanism of the test is not clearly

understood, except perhaps on an allergic basis. The technique is very simple and readily executed, but requires a little experience in reading. The accuracy of the test needs very definitely to be further improved.—Author's Abst.

**Spontanous late descent of the testis.** Drake, C., J. A. M. A. **102:** 759. 1934. Abst., A. M. A.

While making yearly examinations during the past six years of the boys at a country school, the author was impressed by the relative frequency of cases of undescended testis. The boys ranged in age from 9 to 19 years, and out of some 260 boys examined 11 showed this developmental defect. The usual method of palpation with invagination of the scrotum, the examining finger reaching the external inguinal ring, failed to locate the missing testis in any of these 11 boys. Ten of these 12 missing testes have spontaneously descended to the scrotal position. This late spontaneous descent occurred once in the tenth year, twice in the eleventh, twelfth, thirteenth and fourteenth years and once in the sixteenth year. The two persisting cases are in boys now 14 years of age. All except one of the late descended testes have reached the normal position and size. In the boy with a bilateral late descent, the right testis appeared in the scrotum in his fourteenth year and the left in his sixteenth year. While the right testis is normal in size and position, the left is slightly smaller and at present is midsacral in position. The presence of a hernia associated with a late descent of a testis was not determined in a single case, although it is said to be always present. There was no evidence of any lack of physical development in any of these 11 boys. I am assured by the headmaster that none of them show any evidence of being below the average in their studies. From these observations the author concludes that the unilateral uncomplicated undescended testis does not present any surgical problem in spite of considerable medical literature to the contrary. The great majority descend spontaneously by the age of 14, become normal in size and eventually lie low in the scrotal sac. The only case that should be considered a surgical problem is the bilateral one persisting to the fourteenth year or the unilateral case presenting complications.

**Value of Friedman test in diagnosis of intra-uterine and extra-uterine pregnancy.** Goldberger, M. A., U. J. Salmon and R. T. Frank, J. A. M. A. **103:** 1210. 1934. Abst., A. M. A.

The authors point out that in 1093 normal intra-uterine pregnancies the percentage of false positive Friedman tests was 0.09. The percentage of false negatives was 0.55. This small percentage of error as compared to other reports, is attributed to the fact that duplicate tests were performed. At least 3.4% of rabbits appear to be refractory to the Friedman test. In ectopic pregnancy, the percentage of false negatives in a series of 44 cases was 32. The high percentage of negative tests in ectopic pregnancy is accounted for by the presence in these cases of dead or degenerated villi. In both intra-uterine and extra-uterine pregnancies the Friedman test is dependent on the viability of the chorion. In missed abortion the Friedman test may remain positive for as long as 30 days after death of the fetus. In incomplete abortion the Friedman test may be positive. The presence of a viable fetus can be determined by study of the female sex hormone of the blood. In the diagnosis of ectopic gestation the Friedman test is of value only in cases in which it is positive. If the test is negative in a case of suspected ectopic pregnancy, the clinical history and observations should determine the diagnosis.

**Standard metabolism of female rats before and after ovariectomy in experiments with and without narcosis.** Hemmingsen, A. M., Skandinav. Arch. f. Physiol. **67:** 137. 1933. Abst., Chem. Absts. **28:** 1756.

The body temperature of normal rats is subject to so much variation that the standard metabolism must be corrected for temperature. In the rat the standard metabolism seems to vary with the previous environmental temperature. The influence of age is questionable, but the relation between body weight and metabolism varies, especially if standard conditions are not fulfilled. It seems probable that in the rat the standard metabolism bears a definite (proportional) relationship to a fractional power either of the body weight or of the body surface. The influence of the estrous cycle, of ovariectomy and of treatment of spayed animals by ovarian extracts on the standard metabolism has not been satisfactorily solved.

**The hypophyseal-like qualities of the gonadotropic principle found in the urine of certain individuals.** Leonard, S. L. and P. E. Smith, Am. J. Physiol. **108**: 22. 1934.

The physiological action of a follicle-stimulating substance occurring in the urine of a woman past the menopause and who suffered from migraine was studied. Extracts of this urine injected into immature hypophysectomized rats in which a sufficient post-operative period had elapsed for the ovaries to undergo pronounced atrophy, matured a large number of follicles. These follicles were strikingly uniform in size. Even in the longer treatments (10 days) luteinization but rarely occurred. The treatment did not induce an hypertrophy of the interstitial or the theca cells. The reparative effect seemed to be complete. The changes were the opposite in every respect from those induced in hypophysectomized rats by injections of pregnancy-urine extracts. In 2 rats in which an extract of the follicle-stimulating urine was injected, a subsequent intraperitoneal injection of pregnancy urine extract induced ovulation. In one case the number of eggs liberated was greatly in excess of the normal number. Oestrin was produced by the ovaries stimulated with follicle-stimulating urine extract. There was a synergistic action, "augmentation," when an extract of this urine was injected concurrently with a pregnancy-urine extract. In the production of "augmentation" the extract of follicle-stimulating urine can thus be substituted for the pituitary gonadotropic extract. The gonadotropic principle in this follicle-stimulating urine appears to fulfill the requirements postulated for an anterior-pituitary, follicle-stimulating hormone.
—Authors' Summary.

**The exocrine and endocrine functions of the testes.** Lower, W. E., J. Urol. 31: 391. 1934.

By means of parabiosis in an unspecified number of male rats, hypertrophy of the prostate was produced in the normal member after castration in the other member of the pair. There was an overproduction of pituitary hormone following castration which escaped to the control member of the pair by way of the peritoneal fluid and stimulated the reproductive system.—J. C. D.

**The effect on the reproductive organs of the rat of prolonged treatment with ovary-stimulating substances.** McPhail, M. K., J. Physiol. **80**: 105. 1933.

The effects of prolonged injections of extracts of anterior pituitary gland and of pregnant urine have been studied on the reproductive organs of the adult female rat. Fifty rats were thus injected for a period of about six weeks. Some were killed when the injections were discontinued, and others were observed for several weeks thereafter. In the pituitary injected group the ovaries averaged 47 mg. and the uterus 407 mg.; this compares to the means of 116 and 673 mg. for the ovaries and uterus of the urine injected group. The oestrus cycles were partial or entirely inhibited and fertility was decreased. The ovary is probably able to recover comparatively soon from the effects of prolonged treatment with stimulating substances.—F. E. Emery.

**A defeminizing tumor.** Phelan, G. W., Am. J. Obst. & Gynec. **27**: 748. 1934.

The case is reported of a woman of 20 who complained of pain in the lower abdomen. She had never menstruated and since marriage, two years previously, had not experienced normal libido or orgasm. For three years conspicuous growth of hair on the body and face was noticed. The hair distribution was masculine though the skeletal proportions remained feminine. The hips and breasts were flat. The voice was coarse and distinctly masculine. The clitoris was hypertrophied. At operation a small tumor of the left ovary was found. It was diagnosed as arrhenoblastoma. Two months after the operation the patient began to menstruate and two months subsequently became pregnant. To a considerable extent she became feminized: the uterus enlarged and she had to shave less frequently. The body hair became of a fine texture and less luxuriant in growth. The voice was softer, libido was normal and normal orgasm was experienced. The labia were larger but no change could be noticed in the clitoris. She had become "happy and conscious of her feminine self."—R. G. H.

**Metrorrhagias of ovarian origin treated with insulin (Metrorrhagias de origen ovarico tratadas por insulina).** Quadras-Bordes, M. L., Med. ibera, **1**: 777. 1933. Abst., Am. J. Obst. & Gynec. **28**: 263.

Four cases of metrorrhagia are reported, which had been treated with ovarian and thyroid extracts, ergot, calcium chloride, etc. When they did not respond, insulin was given with excellent results. It was found that if insulin was given daily throughout the whole menstrual period in two doses of 20 and 15 units or 20 and 20 units, the hemorrhage ceased and after such treatment for several months insulin could be discontinued. Thirty-five units of insulin in two doses of 20 and 15 units seemed to produce the best results.

**The effect of injection of amniotin on the spontaneous activity of gonadectomized rats.** Richter, C. P. and C. G. Hartman, Am. J. Physiol. **108**: 136. 1934.

Oestrin (5 rat units daily) injected into 7 spayed female rats maintained not only a normal state of the reproductive tract but also a normal level of spontaneous activity. Untreated spayed animals, on the other hand, showed atrophic changes in the tract and became very inactive. Eight castrated males treated with the hormone experienced a similar, though less marked, increase in activity. This effect occurred despite the involution of the male secondary sex glands. The same result was obtained in 7 animals gonadectomized at early ages (1 to 10 days) and injected first at 35 days of age. Inasmuch as oestrin produced a marked increase in the activity of gonadectomized males without preventing the castrate atrophy of the sex apparatus, it is concluded that the hormone contains a factor specific for activity and independent at least in large part of the sex factor.—Authors' Summary.

**Observations on the treatment of infertile rabbits with Antuitrin "S."** Rosahn, P. D., H. S. N. Greene and C. K. Hu, Proc. Soc. Exper. Biol. & Med. **31**: 1008. 1934.

Forty-three trials were made on 27 previously infertile rabbits, each trial consisting of the administration of Antuitrin "S" plus service by a fertile buck. Six deaths followed the administration of the pregnancy urine principle. Nine pregnancies and 28 fertile matings resulted from the 37 trials. During the control period, the 23 animals in the group had been served on 122 separate occasions with 9 pregnancies resulting. The occurrence of pregnancy in relation to the Antuitrin "S" treatment was significantly more frequent than the incidence of pregnancy during the control untreated period. The series was divided into 2 groups depending on the relation of the Antuitrin "S" treatment to the time of mating. In 9 trials the drug had been given from 20-24 hours before the mating—no pregnancies resulted. All 9 pregnancies occurred in the group of 28 trials on 16 animals receiving the drug within 2 hours before to 22 hours after service. These 16 animals had been mated 85 times during the control period and only 2 pregnancies resulted.—M. O. L.

**The toxaemias of pregnancy; the respiratory metabolism.** Rowe, A. W., Mary A. McManus and Gertrude A. Riley, J. Nutrition, **7**: 591. 1934.

The present report deals with an analysis of the respiratory metabolism of a group of 50 pregnant women exhibiting some type of toxaemia complicating the physiological condition. Earlier studies on a larger group of normal pregnant women had defined the characteristic fluctuations of the energy metabolism induced by the progress of pregnancy. Initially the respiratory metabolism remains at the normal level for some 8 or 10 weeks after impregnation; then comes a spontaneous decline to a level inferior to the conventional normal, followed by a slow linear recovery to a point at delivery from 15% to 20% above the minimum. With delivery there is again a decline to subnormal levels followed by a more rapid restoration to the initial norm. Generally speaking, the respiratory metabolism of the toxic group fell well within the range of normal pregnancy. Departures were few in number and were traceable to superimposed effects not demonstrably associated with the toxic condition. The depression of alveolar carbon dioxide tensions characteristic to normal pregnancy were shown in lesser degree in the reports by the toxic cases. Blood pressures, pulse rates, and body temperatures showed concrete changes from those of normal pregnancy, presumably traceable to the toxic status of recovery to normal after delivery was delayed.—Authors' Abst.

**Endocrine factors in the causation of the creatinuria of pregnancy.** Schrire, I. and H. Zwarenstein, Nature, **133:** 27. 1934. Abst., Chem. Absts. **28:** 1756.

After castration or in pregnancy the anterior pituitary gland hypertrophies, increasing the formation of creatine. Stimulation of the gonads inhibits the change of creatine to creatinine; excess creatine appears in the urine as such as well as increasing the creatinine content. Residual corpora lutea re-enforce the inhibitory action of the ovaries on this transformation so the excess creatine is excreted as such, and the creatinine excretion is not increased.

**Pancreatropic action of extracts from anterior lobe of hypophysis (Über die pankreatrope Wirkung von Hypophysenvorderlappenextrakten).** Anselmino, K. J., J. Herold and F. Hoffmann, Klin. Wchnschr. **12:** 1245. 1933.

Clinical observations of others that acromegaly was often accompanied by enlargement of the pancreas and increase in islet tissue and that the anterior lobe eosinophiles were often decreased in juvenile diabetes led the author to try the effect of anterior lobe extract on the pancreas of male rats. The number of animals used is not stated. Typically six injections of fresh aqueous extract of acetone dried powder were given over a period of 3½ days and the animal was sacrificed on the 4th. Changes were found in both the insular and the secretory tissue of the pancreas. Secretory acini with high cylindrical epithelium were found and with increase in the outer zone and decrease in the granular central inner zone. Zymogen granules were decreased. Changes were found in both the insular and the secretory tissue of the pancreas. There was increase in islet number and size; tiny satellite islets were found; the beta cells were more numerous than the alpha cells, and giant nuclei were found. The author interprets these findings as evidence that the anterior lobe extract has increased the functional activity of the insular tissue. Two injections led to increase in islet size in 36 hours but no new formed islets. If sacrifice of the animal was delayed till the 10th day the histological changes found were less marked.—E. C. Albritton.

**Parathyrotropic action of extracts of anterior lobe of hypophysis (Über parathyreotrope Wirkung von Hypophysenvorderlappenextrakten).** Anselmino, K. J., F. Hoffmann and L. Herold, Klin. Wchnschr. **13:** 45. 1934.

The authors describe 3 types of cells in the parathyroid of the rat: (1) large pale chief cells, (2) smaller and darker chief cells, (3) oxyphilic cells (Welch's cells). In the control rats used the second type of cells predominate. When rats are injected with an extract of the anterior lobe of the hypophysis, the pale chief cells increase in number, the dark chief cells are reduced to a small peripheral zone, and the Welch's cells disappear entirely. There is an increase in total size of the gland to 2 or 3 times the normal figure, and a marked distension of capillaries. The method of measuring the glands and the number of cases studied are not given. The conclusion is that the parathyroid is stimulated by a parathyrotropic substance in the anterior lobe of the hypophysis. The authors are inclined to believe that this is a different substance from those which stimulate the gonads, the thyroid, and the pancreas.

—M. M. H.

**Staining the anterior lobe of the hypophysis with Schiff's reagent (La coloration du lobe antérieur de l'hypophyse par le réactif de Schiff).** Bujard, E. and M. Ickowicz, Compt. rend. Soc. de biol. **112:** 1603. 1933.

The fresh anterior lobe from sheep and guinea pigs takes on a violet color when stained with sulphuric acid fuchsin.—J. C. D.

**Posterior pituitary in pyelitis; use of extract for acceleration of drainage and relief of pain.** Darley, W. and W. B. Draper, J. A. M. A. **102:** 677. 1934. Abst., A. M. A.

The authors discuss the therapeutic value of postpituitary extract in pyelitis. Their series consists of 14 adults and 2 children and comprises 7 cases with no history suggestive of a previous pyelitis, 5 of recurrent pyelitis, one of postpartum pyelitis and 3 of post-operative pyelitis. All these patients presented the well defined symptom complex that is characteristic of pyelitis. The diagnosis could have been strengthened by preliminary ureteral catheterization, but the authors were attempting to evaluate a nonsurgical method of drainage and this procedure would have impaired the validity of their control

observations. The solution was administered subcutaneously in doses ranging from 3 to 15 minims (0.2 to 1.0 cc.). The intervals between injections varied from 4 to 18 hours, and they were continued until all signs of acute illness had disappeared. In 9 of the 16 cases the usual medical treatment, including alkalis and urinary antiseptics, had been given a clinical trial for periods ranging from 2 to 28 days (an average of eight days) without relief of pain or other apparent benefit. This is in sharp contrast to the relatively brief interval of from one to four hours (an average of approximately two hours) between the exhibition of the solution and the therapeutic response, as indicated by the relief of pain. The 2 children in whom the time for relief of pain could not be accurately determined presented similar time relationships to the foregoing cases. The remaining patients were ill for an average of only 20 hours before the exhibition of the solution and consequently in this group the customary methods of medical treatment were not given a fair trial. The striking relief of pain noted was in all cases associated with mitigation of such complaints as urinary frequency, dysuria and nausea. Objective improvement was also apparent following the use of the solution. The fever was lowered in two days or less in five cases. Disappearance or diminution of the pathologic elements of the urine often paralleled the clinical improvement but was not a prominent feature of the therapeutic action of the solution. In the authors' opinion, these results are due to accelerated drainage of the upper urinary tract induced by the solution.

**Is an active hormone of the posterior pituitary present in the blood during pregnancy (Gibt es während der Schwangerheit ein aktives Hypophysenhinterlappenhormon im Blute)?** Fekete, K., Endokrinologie, **10:** 16. 1932.

Blood serum from pregnant women was found to inactivate pituitrin when tested on the isolated guinea pig uterus. The effectiveness of the inactivation became greater as pregnancy advanced. Thus, 1 unit of hypophysin was destroyed within 2 hours by 2 cc. of serum from the 8th to 10th month of pregnancy, while only minute traces were destroyed by serum from early pregnancy. Ten cc. of serum from the 9th or 10th month mixed with 1 ampule of "glanduitrin" and allowed to stand 15 hours caused no unusually strong uterine contractions when reinjected. The same amount mixed with non-gravid serum and injected into the same subject produced violent contractions. Using carefully selected uteri of rats, it was found that the addition of 1 cc. of gravid serum to the bath produced no change in contractions, while an equal quantity of non-gravid serum increased the tone of the uterus and the number of contractions. The author concludes that hypophysin is destroyed during pregnancy by some unknown substance acting among other factors which insure the maintenance of pregnancy.—Marie D'Amour.

**Clinical evaluation of the quantitative excretion of Prolan A in teratoma testis.** Ferguson, R. S., J. Urol. **31:** 397. 1934.

In 117 consecutive cases of human teratoma testis, the Prolan A excretion has been followed quantitatively. Its presence and quantity are valuable in diagnosis of this type of tumor and in evaluating the effects of treatment.

—J. C. D.

**Roentgen therapy of pituitary tumors.** Hare, C. C. and C. G. Dyke, Arch. Ophth. **10:** 202. 1933. Arch. Neurol. & Psychiat. **32:** 210.

In this paper, Hare and Dyke discuss their experience with roentgen treatment in 20 cases of pituitary tumor. From a partial review of the literature, the authors draw the conclusion that irradiation may be tried as a first method in the treatment for adenomas of the pituitary gland, that the progress must be carefully and frequently controlled by examination and that, if vision continues to decrease, surgical intervention is indicated. The paper is well illustrated with the fields of the patients, and in many instances with roentgenograms illustrating individual cases. A rather large table analyzes in detail the visual acuity, the visual fields, the accompanying oculomotor palsies and the results observed after irradiation. In 15 patients the general symptoms were relieved, and in 5 there was marked improvement in the visual fields as well as in vision. Five of the 20 patients showed a further diminution of vision after roentgen therapy, and 2 of these were later operated on. Ten of the patients were under observation for from 1 to 4 years. In 1 patient the visual fields and vision became normal, and in 2 the vision and visual fields

showed great improvement. In one of 10 patients who were under observation for one year or less, vision was greatly improved, and in 9 it either remained unchanged or was only slightly improved. The authors' best results were obtained in patients whose visual disturbances were of relatively short duration. Further, although satisfactory results may often be obtained with roentgen treatment, the percentage of patients whose vision was restored was less than that of those operated on. The necessity for repeated examinations of vision and visual fields if roentgen therapy is to be utilized is emphasized; if vision continues to fail, surgical intervention should be undertaken immediately. The authors believe that in a considerable number of cases of adenomas of the pituitary gland, marked improvement occurs in both visual disturbances and general symptoms following carefully given roentgen treatment, therefore roentgen treatment should be tried before surgical measures are decided on.

**"The fat metabolism hormone" and hyperglycemia.** Harrow, B., I. M. Chamelin and A. Mazur, Am. J. Physiol. **109:** 436. 1934.

Out of male urine an extract has been obtained which, when injected into rabbits, causes large increases in blood sugar, acetone bodies and lactic acid, and notable decreases in $CO_2$ combining power. Whatever the substances may be (hormone or otherwise) its effect on carbohydrate and fat metabolism is profound.—B. Harrow.

**Effects of follicle-stimulating and luteinizing pituitary extracts on the ovaries of the infantile and juvenile rabbit.** Hertz, R. and F. L. Hisaw, Am. J. Physiol. **108:** 1. 1934.

The ovaries of 12 four-week-old infantile chinchilla rabbits weighing between 500 and 700 grams remained unmodified after treatment with either follicle-stimulating or unfractionated pituitary extracts in doses which, in juvenile animals between 12 and 14 weeks of age and weighing between 1300 and 1500 grams, invariably elicit a maximal ovarian response. Histological comparison of the infantile and juvenile type of ovary shows the latter to be much more highly differentiated particularly with regard to the formation of antra-containing follicles. The infantile ovary even when grafted under the kidney-capsule of a juvenile host proved unresponsive to pituitary stimulation with the extracts here employed (4 cases). Sixteen juvenile rabbits were given daily subcutaneous injections of a purified follicle-stimulating extract for periods ranging from 5 to 20 days. After 5 days the ovaries were enlarged about five-fold and were made up of large cystic follicles with relatively little interstitial tissue. After about 10 days of continuous treatment the ovaries gradually decreased in size and by the fifteenth day of treatment had receded to approximately their original gross dimensions. This rapid involution was associated with a generalized follicular collapse throughout the ovary and proceeded without intermediate luteinization of the follicles concerned. Nine juvenile rabbits were given daily subcutaneous injections of an unfractionated pituitary extract for periods varying from 5 to 20 days. After 5 days the ovaries increased in size about five-fold and showed extensive luteinization. After about 10 days the ovaries gradually decreased in size and by the 15th day had reached practically their original gross dimensions. This involution was associated with a disintegration of the experimentally produced corpora lutea and an excessive deposition of interstitial tissue. Eight rabbits whose ovaries had been rendered refractory to further pituitary stimulation by prolonged treatment were allowed to remain untreated for 2 to 3 months. At the end of this time a second treatment showed that the ovaries of none of these animals had recovered their responsiveness to hypophyseal stimulation. Twenty-one juvenile rabbits were given subcutaneous injections of a luteinizing extract for 5 days. Nineteen of these animals showed very slight ovarian enlargement and several corpora lutea. The ovaries of the remaining 2 animals were unaffected. Successive treatment with follicle-stimulating and luteinizing extracts in 31 juvenile rabbits elicited ovarian enlargement and extensive luteinization with ovulation in 14, ovarian enlargement and extensive luteinization without ovulation in 12, and only follicular development and ovarian enlargement in 5. Preliminary treatment with a subthreshold dose of follicle-stimulating extract rendered 14 juvenile rabbits insensitive to even maximal doses subsequently administered. Discussion is given concerning the bearing which the present work has upon: (a) the problem of the prepubertal conditioning of the ovary; (b) the occurrence of gonadal

hypoplasia in clinical cases of hyperpituitarism; (c) the progress of senility despite the continuation of hypophyseal secretion; (d) the physiology of ovulation; (e) the question of the duality of the gonadotropic pituitary hormones. —Authors' Summary.

**Action of extracts of anterior lobe of hypophysis on calcium content of blood (Über die Wirkung von Hypophysenvorderlappenextrakten auf den Blutkalkspiegal).** Hoffman, F. and K. J. Anselmino, Klin. Wchnschr. **13:** 44. 1934.

Dogs were injected with an extract of the anterior lobe of the hypophysis. The treatment caused a rise of blood calcium to a level of 12.5, eight or nine hours after the injection. In 10 normal rats, similarly injected, the calcium level at three to six hours ranged from 11.6 to 12.3, with an average of 11.9. The calcium in the 8 controls averaged 10.6. These results are compared with the figures obtained from parathyroidectomized rats, injected and not injected. In the latter, the calcium level was 9.2 (9 cases, ranged from 8.4 to 11.2). In the 5 parathyroidectomized animals which were injected with hypophysis extract the calcium level at three to four hours averaged 9.4. The authors conclude that the extract of the anterior lobe of the hypophysis affects the blood calcium through the medium of the parathyroid.—M. M. H.

**Clinical and experimental studies on the thyreotropic hormone of the anterior pituitary (Klinische und experimentelle Untersuchungen über das thyreotrope Hormon des Hypophysenvorderlappens).** Horsters, H., Arch. f. exper. Path. u. Pharmakol. **169:** 537. 1933.

The injection of 50 units of thyreotropic hormone (Schering-Kahlbaum) into rabbits (2) which had been fasted 24 hours caused a lowering of the blood sugar of 40% in 180 minutes. This did not occur in rabbits (2) not fasted. Seven patients with pathological conditions such as diabetes mellitus, abdominal tuberculosis, catarrhal jaundice, subacute liver atrophy and arteriosclerosis, were given large doses (500 units) of thyreotropic hormone. The patients with liver damage showed a lowering of the blood sugar within 60 minutes after subcutaneous injection which remained low during the second hour. The greatest drop in blood sugar (44 mg. per cent) occurred in a patient with catarrhal jaundice. In certain cases of diabetes a fall of blood sugar occurred. When thyreotropic hormone was given over a period of time an improvement in carbohydrate assimilation occurred. A diabetic patient, 20 years of age, was given thyreotropic hormone in doses of 200 units for 9 days. The blood sugar dropped from 273 mg. per cent to 112 mg. per cent; the glycosuria decreased from 40 gm. to 7 gm. per day. The diet was kept the same and no insulin was given. It is suggested that the thyreotropic hormone is tied up with the hypophyseal form of diabetes mellitus. The patients with impaired liver function showed a retention of NaCl and uric acid when the thyreotropic hormone was given for a period of time. Calcium retention occurred in 4 patients. The thyreotropic hormone caused a fall in blood pressure both in patients and in healthy individuals, which reached its lowest point 40-60 minutes after the subcutaneous injection. The intravenous injection of thyreotropic hormone in the dog had no appreciable effect upon the blood pressure, but it had a significant antagonistic effect upon the vasopressor substance, "Tonephin."—E. M. Anderson.

**Diabetogenic activity of anterior pituitary extract (Propiedades diabetogenas del extracto antero-hipofisario en diversas condiciones).** Houssay, B. A., A. Biasotti and C. T. Rietti, Rev. Soc. argent. de biol. **9:** 489. 1933.

Alkaline anterior pituitary extract was injected intraperitoneally in daily doses varying from 1.4 to 10 grams fresh lobe. Hyperglycemia was observed in cats, dogs, pigeons, guinea-pigs, rats, rabbits and mice (in order of decreasing effect) but not in toads (Bufo arenarum) nor in a snake, Ophis merremi. In dogs on a carbohydrate diet hyperglycemia, glycosuria and hyperlactacidemia were more pronounced than when they were on a meat diet. Extracts of muscle, kidney, thyroid, testicle, spleen, liver and posterior pituitary lobe according to the method of Evans and Simpson did not have a diabetogenic activity, and neither did the acetic extract of posterior pituitary lobe standard powder. Castration, extirpation of the adrenal medulla, section of splanchnic nerves with extirpation of the lumbar sympathetics and lesions of the tuber cinereum did not modify the response to the extract. Thyroidectomy slightly diminished the increase in blood sugar and glycosuria. The activity of the

extract is gradually lost on heating from 55° C. to 80° C. It is soluble in 50% alcohol, it does not pass ultrafilters; it could not be satisfactorily separated by adsorption and elusion; it is partially precipitated by 30% sodium sulphate.
—J. T. L.

**Blood cholesterol and hypometabolism; suprarenal and pituitary deficiency, obesity and miscellaneous conditions.** Hurxthal, L. M., Arch. Int. Med. **53:** 825. 1934.

The author has investigated the level of blood cholesterol in various conditions characterized by hypometabolism in which the thyroid gland did not appear to be involved. In 2 cases of Addison's disease with low metabolic rates there was no elevation of the blood cholesterol. In 5 cases of proved pituitary (chromophobe) adenomas with subnormal metabolic levels, the blood cholesterol was above 200 mg. in only one, a female in whom the value was 229 mg. In 25 patients with obesity, hypometabolism was usually found accompanied by a normal blood cholesterol. In 55 patients suffering from miscellaneous clinical conditions characterized by low metabolism normal blood cholesterol values were obtained. His conclusion is that hypometabolism not accompanied by hypercholesteremia is probably not due to thyroid failure.
—H. Freeman.

**Action of anterior pituitary lobe extract upon the thyroid (Die Wirkung des Hypophysenvorderlappens auf die Schilddrüse).** Janssen, S. and A. Loeser, Arch. f. exper. Path. u. Pharmakol. **163:** 517. 1931.

Specific alterations were produced in the thyroid by injections of anterior pituitary lobe extract in young guinea pigs and young dogs. These consisted of the formation of vacuoles and the disappearance of stainable colloid. There was no effect when the extract was administered orally. The results were independent of the action on the gonads.—M. O. L.

**The hormone action of the hypophysis on the adrenals (Das interrenotrope Hormon der Hypophyse).** Jores, A., Klin. Wchnschr. **12:** 1989. 1933. Abst., Physiol. Absts. **19:** 194.

A protein-free solution of the melanophore hormone was injected into 4-weeks-old rabbits on 5 occasions during 10 weeks. The adrenals of the injected animals weighed 12.2 mg. per 100 gr. body weight, those of the controls 0.4 mg. per 100 gr. Histological examination showed a hypertrophic cortex and a greater amount of adrenaline. These results are in harmony with the previous investigations of the author, showing that the basophil cells of the hypophysis form the melanophore hormone, and with the findings of Kraus that these cells exhibit a relation to the adrenals.

**Anterior pituitary extract and iodine content of the thyroid (Hypophysenvorderlappen und Jodgehalt der Schilddrüse).** Loeser, A., Arch. f. exper. Path. u. Pharmakol. **163:** 530. 1931.

Injection of anterior pituitary extract caused a marked diminution of iodine in the thyroid of young dogs as well as morphologic alterations.
—M. O. L.

**Anti-insulin hormone of anterior pituitary (Das kontrainsuläre Hormon des Hypophysenvorderlappens und seine Stellung zu anderen Hormonwirkungen dieses Organs).** Lucke, H., Arch. f. exper. Path. u. Pharmakol. **170:** 166. 1933. Abst., Physiol. Absts. **19:** 56.

A hormone produced in the anterior pituitary is specifically concerned with carbohydrate metabolism, acts as an antagonist to insulin, and is therefore so designated. It is identical with the pituitary substance, which accentuates pancreatic diabetes. It is distinct, according to ultra-filtration tests, from the fat metabolism hormone. It is not identical with the thyreotropic hormone, because its action is not linked with that of the thyroid, and also because the thyreotropic hormone in its pure state causes no hyperglycaemia, even in large doses. The anti-insulin hormone is not identical with the gonadotropic hormone, because pregnancy is accompanied by no signs of increased or altered production of the anti-insulin hormone. There is no possibility at present of separating the growth hormone from the anti-insulin hormone. Extracts of the anterior pituitary which contain the one, contain also the other. The two may be closely related or may be identical.

**Hypoglycemia hypophysiopriva.** Mahoney, Wm., Am. J. Physiol. **109:** 475. 1934.

Puppies ranging from 5 to 10 weeks of age were used in these experiments. Following the intraperitoneal administration of sodium amytal—and with the additional help of hypertonic sodium chloride intravenously, the hypophysis was removed, using a right subtemporal approach. Puppies were selected because the stunting of growth served as a criterion of complete hypophysectomy. The state of cachexia hypophysiopriva following the removal of the hypophysis has been attributed by many workers as being due to operative trauma. In this series no demonstrable lesion of the hypothalmus was observed. The train of symptoms following hypophysectomy resembled the hypoglycemic crisis of man. Administration of glucose raised the blood sugar and resuscitated the animals in the advanced state of cachexia. In fasting puppies the physical signs of hypoglycemia appear within 24-26 hours after hypophysectomy at a blood sugar level of 50 mg. (Benedict-Folin-Wu), following this the blood sugar curve falls to zero. Repeated administration of carbohydrates prevented the appearance of the usual train of symptoms which characterize cachexia hypophysiopriva.—L. B. Shpiner.

**Basophilic syndrome of the pituitary; pituitary basophilism (Cushing).** Pardee, I. H., Arch. Neurol. & Psychiat. **31:** 1007. 1934.

The author presented a brief résumé of the case histories and studies on seven of his patients, all of whom presented clinical signs and symptoms similar to those patients whom Cushing described in his monograph on "Pituitary Basophilism." All of Pardee's patients are alive and showed adiposity. One had abdominal girdle obesity. All complained of headaches and fatigability. All patients had torsos much longer than normal in relationship to their leg lengths. Hypertrichosis was found in six patients; vascular hypertension in six; osteoporosis in three, and three had signs of increased intracranial pressure, i.e., exophthalmus, polyuria and disturbances of visual fields. Amenorrhea was present in two patients and oligomenorrhea was found in three. Polycythemia was found in two patients; low sugar tolerance in two others. X-ray radiation directed towards the pituitary body was given to three of the patients. This was followed by a marked relief of symptoms in two and a slight relief in one.—W. Freeman.

**Action of anterior pituitary lobe and tuber cinereum extracts on seminal vesicles (Sostanze ad azione ormonica preipofisaria nel' tuber cinereum e nel liquor ventricolare dell'uomo).** Pighini, G., Biochem. e terap. sper. **19:** 257. 1932.

In prepuberal male and female rats the maturation of the seminal vesicles and the ovarian follicles was hastened by treatment with extracts of the anterior lobe of the hypophysis and by extracts of the tuber cinereum. Similar results were obtained with liquid removed from the cerebral ventricles of human cadavers. There was no reaction obtained with extracts of cerebral cortex of man, of tuber cinereum of beef and cerebro-spinal fluid collected from man by lumbar puncture.—M. O. L.

**Chorio-epithelioma and the Aschheim-Zondek test; case (Chorioepitelioma com Aschheim-Zondek positivo).** Sá, P., Rev. de gynec. e d'obst. **27:** 306. 1933. Abst., J. A. M. A. **101:** 1682.

Sá states that the concentration of hypophyseal hormones in the urine of pregnant women is lower than that in the urine of women having uterine mole or cholio-epithelioma. The persistence of positive results of the Aschheim-Zondek test with a concentration in hormones higher than that which may be an indication of an intercurrent pregnancy, following a molar abortion either complete or completed by means of curettage, is a diagnostic sign of the presence of chorio-epithelioma and a therapeutic indication for the performance of a total hysterectomy, even in young women. The author's patient, aged 22, had an incomplete hemorrhagic molar abortion, which was finished by means of curettage. The hemorrhage ceased and the patient was discharged from the hospital, apparently cured. After this event, however, she presented a condition of incipient cachexia. The Aschheim-Zondek test, performed 38 and 53 days after the molar abortion, gave position results with a high concentration of prehypophyseal hormones. Total hysterectomy was followed by complete

recovery. The patient gained weight and there was a great improvement in her general condition. This improvement has persisted one year after the operation and no metastases have appeared. The histologic study of the uterus removed at the operation gave a diagnosis of chorio-epithelioma.

**Some considerations on the pathogenesis of diabetes insipidus.** Salmon, A., Schweiz. Arch. f. Neurol. u. Psychiat. **33:** 95. 1933; Abst., Arch. Neurol. & Psychiat. **32:** 644.

Diabetes insipidus is generally transitory following experimental injury of the tuber cinereum and may be lacking altogether when the entire floor of the third ventricle has been destroyed by disease. There are no constant relations, furthermore, between polyuria and either hypofunction or hyperfunction of the anterior lobe of the hypophysis. Salmon seeks, with the aid of numerous citations from the literature, to account for these discrepancies. Normal urinary secretion, he assumes, is dependent on the existence of a proper balance between the respective functional states of the sympathetic and parasympathetic systems. In the presence of a lesion sufficiently extensive to destroy the hypothalamic centers of both systems, diabetes insipidus would, according to this hypothesis, be lacking. The vegetative equilibrium is further assumed to be related to a "hormonal equilibrium." After citing instances of an antagonism between the respective actions of solution of pituitary and epinephrine, the author points out that the latter, when given in small doses, may act as a vasodilator and diuretic, particularly in vagotonic states or states of depressed sympathetic activity. Injections of epinephrine often aggravate a pre-existing polyuria, and autopsy has revealed, in cases in which the polyuria ceased in the terminal stages, changes in the suprarenal glands as well as in the hypophysis.

**The pressor and oxytocic content of the hypophysis of rats under various conditions.** Simon, A., Am. J. Physiol. **107:** 220. 1934.

The hypophyses of 7 normal rats were assayed by the uterus method. Each was found to contain about 0.8 unit of the pressor and oxytocic principles. The amount of both principles was largely independent of the weight of the animal. The ratio pressor principle:oxytocic principle was always the same as in the standard powder. In the hypophyses of 11 rats kept on a diet deficient in water for a period of 5 to 7 days, there was found a large decrease in the content of both the pressor and oxytocic principle. Fasting for a week, fighting and electric stimulation, forced muscular work, adrenalectomy, the intraperitoneal administration of large amounts of 0.9% NaCl solution for several days, did not appear to influence the pressor and oxytocic activities of the hypophysis.—R. G. H.

**Antagonistic action of new pancreas extract on thyrotoxicosis (Die antagonitische Wirkung eines neuen Pankreasextraktes auf die Thyroxinvergiftung).** Balo, J., L. Lovas, E. Bach and L. Neufeld, Arch. f. exper. Path. u. Pharmakol. **165:** 594. 1932.

The preparation of a pancreatic extract which protects the rabbit against a fatal dose of thyroxine and which prevents the lowering of the lipase content of the serum is described. The active principle of this extract is heat stable, shows none of the properties of an albumin and causes, when injected alone, an increase of serum lipase. In contrast to insulin it has no hypoglycemic action. The authors call the active substance "retardine" and consider it to be a hormone.—M. O. L.

**The sexual variation in carbohydrate metabolism; the metabolism of diacetic acid in fasting rats and guinea pigs.** Butts, J. S. and H. J. Deuel, Jr., J. Biol. Chem. **100:** 415. 1933.

No sexual variation has been noted in the small excretion of acetone bodies which occurs during fasting in rats. When diacetic acid is fed by stomach tube to fasting rats and guinea pigs as the sodium salt in an amount of 1.5 mg. per sq. cm. of body surface daily, considerable amounts are excreted in the urine. About twice as much is eliminated by the females as by the males. The difference tends to become exaggerated as the fast progresses. This ketonuria is a physiological phenomenon, as it is greatly decreased by the ingestion of carbohydrate. Earlier results on humans have shown a much

readier susceptibility of women to fasting ketosis than is true with men. It is suggested that a fundamental difference in carbohydrate metabolism, which is generalized in its occurrence, obtains between the sexes.—Authors' Summary.

**The influence of the vagus nerves on the secretions of insulin.** Clark, G. A., J. Physiol. **73:** 297. 1931.

Numal anesthesia given together with intravenous injections of glucose prolonged hyperglycemia in the rabbit. Glucose tolerance, after numal, was increased in two cases 7 to 10 days after section of both vagi below the diaphragm. In the cat the tolerance was increased 2 to 3 hours after section of the right vagus and was not modified after section of the left below the diaphragm. Section of the right vagus below the diaphragm in the cat anesthetized with numal or chloralose caused a rapid fall of blood sugar. This confirms experiments of others and indicates the presence of fibers conveying tonic inhibitory impulses to the islands of Langerhans.—M. O. L.

**Diabetic lipaemia; rôle of the fats in diabetes mellitus, with a description of the haemolipokrit method for the estimation of fat in the blood serum.** Collins, D. H., Quart. J. Med. **2:** 267. 1933.

This article records the results of serum-fat estimations on 103 diabetic and 55 non-diabetic blood samples. Rückert's haemolipokrit method, described in 1931, for the volumetric estimation of fat in blood serum, is utilized. The author discusses this simplified procedure of determining serum fat and after several confirmatory experiments made to estimate the relation the volumetric lipokrit results bear to those obtained by more elaborate gravimetric methods, recommends its use. Data obtained by this apparently reliable technique, in general bear out the conclusions attained by other workers notably Joslin, Bloor and Gray. Increase of the serum-fats is associated with the presence of glycosuria and acetonuria and with the clinically severe cases of diabetes in particular. Also no clear relationship could be established between the serum-fat and the blood sugar level, or the body weight of the patient. Finally in discussing the possible explanations of the cause of the increase of fats in the blood in diabetes he expresses an opinion that the lipemia of diabetes is solely dependent on the inhibition of carbohydrate metabolism and that the increased amount of fat in the blood is evidence of a mobilization of fat in response to the calorific requirements of the body.—H. C. Shepardson.

**Histology of the islands of Langerhans and experimental modifications of the glycemia (Sulle modificazioni istologische delgi isoletti pancreatici nella iperglicemia e nella ipoglicemia sperimentali).** Corpaci, A., Sperimentale, Arch. di biol. **86:** 129. 1932.

In experimental hyperglycemia in the rabbit obtained directly or indirectly by the prolonged administration of glucose or adrenaline there was noted an increase in the volume of the islands of Langerhans and in those elements only; on the contrary, in hypoglycemia produced by insulin administration the volume of these islets was diminished. The histologic modifications were: a disappearance of the cellular limits in hyperglycemia with a greater diminution of volume of the cytoplasm, and pycnosis of the nuclei. In hypoglycemia the volume of the cytoplasm is increased, the cellular boundaries are distinct and changes in nuclei are rare. In an animal rendered artificially hyperglycemic there occurs an abundant formation of new acidiphile cells in the islands by direct transformation of the exocrine elements of the pancreas. —M. O. L.

**The physiological activation of insulin.** Himsworth, H. P., Clin. Sc. **1:** 1. 1933.

Capillary and venous blood sugar curves (50 gm. glucose) were obtained on 5 healthy young men who were on weighed high carbohydrate or high fat diets. Blood sugar was determined at 6 to 10 min. intervals, later in the curve 15 min., using the Hagedorn-Jensen method. The difference between the glucose content of the two sample at any particular point in the curves is considered an indication of the active insulin present in the tissues. The sugar content of venous blood was found to parallel that of capillary blood save at a point shortly after the beginning of the hyperglycemia. Here an S-shaped deviation has been demonstrated by 3 consecutive variations, the last so

marked it is termed the "venous step." This step, ascribed to secretion of pancreatic insulin, develops earlier in the high carbohydrate experiments. With intravenous insulin (2.5 units crystalline insulin as standard dose), there is a shorter latent period and more rapid fall in blood sugar with the high carbohydrate or after repeated glucose ingestion than with the high fat diets. The action of insulin is this: following a short latent period, it manifests its action with increasing velocity; the duration of the latent period and the time the blood sugar reaches its minimum are independent of the units injected; increase in insulin produces a corresponding increase in rate of blood sugar fall; however, above a critical dosage point, no further increase of insulin results in acceleration of depression. In explanation: (a) insulin as prepared and secreted endogenously is inactive; (b) it is activated in an autocatalytic reaction with an unknown factor, which (c) behaves as a kinase and insulin as a substrate. An association of liver injury or disease with kinase production may obtain.—R. B. Gibson.

**The assay of insulin and the blood sugar level.** Hrubetz, M. Caroline, Am. J. Physiol. **107:** 284. 1934.

Four hundred and eighty-one observations were made upon normal-fed rats in 5 series of approximately 100 each. Mean blood sugar levels of from 89 to 112 mg. were obtained. Eight hundred and three observations made during inanition showed a progressive fall in the blood sugar level through the first 24 hours; after which the blood sugar level tended to become constant. No correlation between the blood sugar level and age, sex or weight could be demonstrated. Nine hundred and fifty-one observations on the fall in the blood sugar level one-half hour after the injection of insulin in doses ranging from $\frac{1}{32}$ to 4 units per kilo are presented. With doses less than one-half unit per kilo the percentage drop is a logarithmic function of the dosage within the range studied. The results of 1000 observations on the incidence of shock after varying doses of insulin are reviewed. It is suggested that the initial fall in the blood sugar level one-half hour after the injection in doses smaller than one-half unit per kilo be used in the assay of insulin. This supposition is made because the effects more closely simulate those sought for in the clinical use of insulin, and because of the greater reliability in measuring the results of such doses.—Author's Summary.

**The effect of insulin and other factors on iodo-acetate hyperglycemia.** Irving, J. T., J. Physiol. **80:** 360. 1934.

In 1932 Irving showed that iodo-acetic acid, in toxic doses, caused a fairly pronounced hyperglycemia in rabbits. The present article details a group of experiments carried out in an attempt to elucidate the basis of this effect. The acid used was recrystallized from hot petroleum ether. The necessary amount was dissolved in distilled water. The method of sugar estimation used was that of Hagedorn and Jensen. The animals used were rabbits which had been starved overnight and the injections were subcutaneous. The hyperglycemia always caused by lethal doses of iodo-acetate were shown to be largely inhibited by ergotoxine and completely annulled by pituitrin, without altering the toxicity of the acid. Also iodo-acetic acid usually reverses or prevents insulin hypoglycemia. However, by using appropriate doses, it was possible to obtain a hypoglycemia without affecting the toxic effect of the acid. In addition iodo-acetic acid markedly inhibits the utilization of sugar by the tissues in the absence of insulin. When insulin was present this inhibiton was less pronounced. Irving concludes that iodo-acetic acid causes hyperglycemia by mobilizing liver glycogen and interfering with the disappearance of sugar in the tissues.—H. C. Shepardson.

**Relation of the duodenal mucosa to the internal secretion of the pancreas.** Laughton, N. B. and A. B. Macallum, Proc. Roy. Soc. London, s. B. **111:** 37. 1932.

A material was prepared from the duodenal mucosa of rabbits, dogs, hogs, and cattle. It did not excite pancreatic secretion nor cause hypoglycemia; it did not reduce the hyperglycemia of depancreatized dogs; but it did reduce the hyperglycemias produced by the injection of epinephrin and the administration of glucose.—F. T. Jung.

**Insulin resistance in diabetes mellitus.** MacBryde, C. M., Arch. Int. Med. **52:** 932. 1933.

Attention is called to the frequency of occurrence of relative resistance to insulin in uncomplicated cases of diabetes mellitus. Clinical studies of 2 cases of insulin-sensitive and 3 cases of insulin-resistant diabetes are reported. In 2 of these patients resistance to endogenous insulin was apparently broken, an overdosage of insulin being followed by marked improvement in carbohydrate tolerance. The clinical characteristics of the insulin-resistant type as distinguished from the insulin-sensitive type are outlined. Reported cases of insulin resistance may be grouped as follows: (a) Unexplained, such as 5 cases reported in the paper. Insulin resistance is usually of mild or moderate degree in this group. Hyperactivity of the suprarenal-sympathetic system is suggested as the cause of this type of resistance. Many of these patients might be termed constitutionally resistant. (b) Infection. (c) Destructive pancreatic disease. (d) Disorders of other endocrine glands, particularly the thyroid, pituitary and suprarenal glands. (e) Hepatic disorders. (f) Miscellaneous conditions such as acidosis, coma, disease of the skin and cardiac decompensation. The value of determining the relative responsiveness to insulin for treatment as well as for further study of diabetes is emphasized. —Author's Summary.

**Abdominal symptoms with or without abdominal lesions in diabetic acidosis.** McKittrick, L. S., New England J. Med. **209:** 1033. 1933.

Attention is called to the difficulty in differentiating abdominal pain due to impending coma from that caused by a surgical lesion in the abdomen. Case histories are cited and general rules of procedure given. The author believes that one is justified in saying that a history of malaise, drowsiness, vomiting, diffuse abdominal pain, associated with wide-spread tenderness, and spasm is so suggestive of diabetic acidosis, without demonstrable intra-abdominal disease that operation should not be performed unless the abdominal symptoms persist after three or four hours of adequate insulin treatment. Conversely, a history of abdominal pain with or without vomiting, when associated with localized and definite abdominal tenderness, usually with spasm, is suggestive of a surgical lesion within the abdomen in the patient with diabetic acidosis, just as it is in the non-diabetic, and may be an indication for immediate operation. In that rare case, where definite differentiation is impossible and yet imperative, it may be safer to open the abdomen under local anesthesia than to suffer further delay.—J. C. D.

**Note on the histo-chemistry of the arteries from diabetics (Contribution à l'étude histo-chimique des artérites diabétiques).** Rathery, F. and S. Doubrow, Compt. rend Soc. de biol. **113:** 56. 1933.

In incineration tests, sections of arteries embedded in paraffin incinerated much more rapidly than those from arteries simply coagulated. This was due to loss of fat during the embedding process. A micro-chemical analysis showed that in the diabetic arteries the intima was rich in stearates and palmitates, the media was relatively free from fats, while the adventitia contained oleates. —J. C. D.

**Abnormalities of calcium deposition in diabetes mellitus.** Root, H. F., Priscilla White and A. Marble, Arch. Int. Med. **53:** 46. 1934.

Disturbance of the calcium metabolism in diabetes was observed in various tissues. Two cases of spontaneous fractures of the vertebrae are reported together with fractures occurring elsewhere after very slight injury. Thinning of the bones was reported in a series of cases and actual atrophy of the bone was noted in 11% of 100 x-rays. Calcification of the arteries has frequently been noted. Decalcification of the teeth occurs especially in cases of uncontrolled diabetes. In one instance a diabetic boy had lost all his teeth by the age of 17 years. A loss of calcium in the body occurs during acidosis and in diarrhea. It is important to remember that the diet may be deficient in calcium if a diet extremely low in fat is planned since this will include little milk or cream. Adequate treatment with insulin prevents these abnormalities of calcium metabolism, because it controls the diabetes.—H. F. Root.

**Neurologic manifestations of hyperinsulinism and other hypoglycemic states.** Rynearson, E. H. and F. P. Moersch, J. A. M. A. **103:** 1196. 1934. Abst., A. M. A.

The authors limit their discussion to conditions that are the antithesis of diabetes, in which symptoms are produced by an insufficiency of sugar in contrast to an excess and they concentrate their attention more on symptoms than on pathologic conditions or on treatment, and especially on the preponderance of neurologic symptoms in these conditions. They emphasize the universal occurrence of neurologic and psychic symptoms in severe hypoglycemia and hope that through the cooperation of neurologists and psychiatrists many heretofore undiagnosed cases of hypoglycemia may be discovered. In the light of present inadequate knowledge, medical treatment is unsatisfactory, and it is only by early surgical exploration in these cases of hypoglycemia that adenomas of the island cells of the pancreas may be found and successfully removed. It is to be hoped that it will be possible to separate accurately the various types of hypoglycemia and to treat each type better.

**The histopathology of experimental insulin intoxication (Beiträge zur Histopathologie der experimentellen Insulinvergiftung).** Stief, A. and L. Tokay, Ztschr. f. d. ges. Neurol. u. Psychiat. **139:** 434. 1932. Abst., Arch. Neurol. & Psychiat. **31:** 862.

Insulin intoxication was produced in 4 rabbits and 4 dogs. In the former the period of intoxication lasted from 8 to 10 weeks, and the clinical symptoms were few. They were more pronounced in the dogs and consisted of sialorrhea, perspiration, tremors, spasms, epileptiform attacks and catatonic and cataleptic postures. Grossly, the brains showed no abnormalities except extreme dryness and a tendency to break. The histologic findings were similar in rabbits and dogs. In general the nerve cells showed the severe changes of Nissl, with areas of sclerotic nerve cells and cells with acute and chronic changes. The glia took little part in the process, but in some places there was a reaction of the oligodendroglia and microglia. There were areas in which a marked mesodermal proliferation had taken place, with an increase in the number of capillaries. While the changes were diffuse, there were also focal changes. There were cortical areas in which the upper cortical layers were destroyed, others in which the lower layers were gone, and still others in which complete sectors had disappeared. In the rabbit the temporal lobes were most severely involved. In the basal ganglia the putamen and caudate were severely involved, while the pallidum showed but slight changes. The nuclei supraopticus and paraventricularis were severely involved. The vessels were hyperemic everywhere, especially in the hypophysis. There were small hemorrhages in the infundibulum. The changes in these cases are not specific. They are present in other intoxications, such as morphinism and uremia. There is a certain resemblance to the changes occurring in lead and guanidine intoxications. Besides the general intoxication, circulatory disorders play a rôle, as indicated by the lamellar degenerations in the cortex. Such disturbances have been postulated in man because of the presence of symptoms such as aphasia and hemiplegia. Redisch was able to observe with the capillary microscope arterial spasm and dilatation in cases of hypoglycemia. Some investigators believe that the changes in the brain are the direct result of the insulin; others attribute them to the hypoglycemia.

**Pseudoxanthoma elasticum associated with angioid streaks of the retina and diabetes mellitus in sisters.** Sugg, E. S. and D. D. Stetson, J. A. M. A. **102:** 1369. 1934. Abst., A. M. A.

The authors add their two cases occurring in sisters, who also have diabetes mellitus, to the 17 cases already reported of pseudoxanthoma elasticum associated with angioid streaks of the retina. No evidence as to the etiology of pseudoxanthoma elasticum has been discovered. Some writers express the belief that a hereditary predisposition is present, and other express the opinion that, because of the close resemblance to senile elastosis, pseudoxanthoma elasticum is an evidence of presenility. No satisfactory pathologic examination has ever been made of angioid streaks of the retina, and the etiology is unknown. The latest suggestion is that it is a part of a generalized process of elastic tissue degeneration, involving the skin, circulatory system and eyes. The disease is progressive, and sooner or later vision is impaired. There has been reported no satisfactory treatment. An insufficient number of cases of

diabetes mellitus in combination with pseudoxanthoma elasticum has been reported to be of significance, except that the familial tendency of diabetes mellitus is well known, and pseudoxanthoma elasticum has been reported in other members of the same family. The occurrence of pseudoxanthoma elasticum and angioid streaks of the retina in the same patients is frequent and striking, but the authors are unable to agree that a new disease has been established. No treatment of pseudoxanthoma elasticum has met with any success except in the case reported by Lewis and Clayton, in which the skin of the neck was apparently improved by means of roentgen rays.

**Hypoglycemia due to adenoma of the islets of Langerhans.** Womack, N. S., South. M. J. **27:** 134. 1934.

The report is based on five cases treated successfully by surgical removal of the adenoma. The main symptoms were gradual onset with periods of hunger, dizziness, and momentary loss of consciousness with automatic movements. The attacks were associated with periods of starvation. Attacks became progressively more frequent and severe. Hypoglycemia and high sugar tolerance were found. Surgery was very successful and should be resorted to early to prevent the mental deterioration associated with repeated attacks.
—J. C. D.

**Some atypical responses of rabbits to insulin.** Zeckwer, I. T., Am. J. Physiol. **106:** 273. 1933.

Six of a series of 40 unselected rabbits showed resistance to doses of insulin larger than those causing convulsions in any normal rabbit, while 3 showed slight resistance. This tolerance varied up to 66 units, and seemed to be dependent upon a spontaneous resistance which could be increased to some extent by subjecting the rabbits to ascending non-convulsant doses. Refractory rabbits injected with large doses of insulin showed a rapid fall in blood sugar, which remained low for many hours, followed by spontaneous recovery without the administration of glucose. After thyroidectomy, 2 very resistant rabbits showed increased sensitiveness to insulin varying from 10 to 20 fold, while 4 normal control rabbits showed an increased sensitiveness after thyroidectomy of 2.5 to 4.6 fold. However, the resistant rabbits after thyroidectomy never showed convulsions with the minute doses of insulin to which normal rabbits respond after thyroidectomy. That is, a considerable residual resistance to insulin remains after thyroidectomy in the very refractory rabbits. The thyroids of resistant rabbits showed no gross or microscopic deviation from normal. The relation of refractoriness to activity of the sympathetic nervous system is discussed.—Authors' Summary.

**Hyperparathyroidism; a common and polymorphic condition as illustrated by seventeen proved cases from one clinic.** Albright, F., J. C. Aub and W. Bauer, J. A. M. A. **102:** 1276. 1934. Abst., A. M. A.

It is the object of the authors to point out that other forms than osteitis fibrosa cystica of hyperparathyroidism are not rare pathologic curiosities but conditions that every practitioner will not infrequently meet. The diagnosis must be considered and ruled in or out when any of a whole list of presenting symptoms of the most varied nature is encountered. They present 17 cases that form the basis of their study in all of which a parathyroid tumor was removed in each instance. They can only partially account for the large series by the fact that a special study on bone metabolism was being conducted. They divided the symptomatology into that due to hypercalcemia alone, that related to skeletal changes and that related to the increased excretion of calcium and phosphorus in the urine, and in their discussion they lay emphasis on the different forms which the disease may take, the pathologic changes and pathologic physiology, the signs and symptoms, the laboratory diagnosis, the roentgen diagnosis, the treatment and the differential diagnosis. They wish to stress the point that, whereas the disease can hardly be called common, it must frequently be considered when any of a multiplicity of symptoms is present. Failure to make the diagnosis is regrettable in that therapy for it is highly successful. Of the 17 cases three were of the classic type, six presented nephrolithiasis, two were osteoporotic with nephrolithiasis, one osteoporotis, one nephrocalcinotic, one classic with nephrolithiasis, one classic with nephrocalcinosis and nephrolithiasis, one simulated Paget's disease with nephrolithiasis and one was osteoporotic with nephrocalcinosis.

**A study of the effects of hypercalcaemia produced by parathyroid hormone and irradiated ergosterol upon the activity of the cerebral cortex by means of conditioned reflexes.** Andreyev, L. and L. I. Pugsley, Quart. J. Exper. Physiol. **24:** 189. 1934.

Report is made of about 700 experiments on two dogs. Conditioned reflexes of the salivary glands were used. Several different conditioning stimuli were employed. It was found that hypercalcaemia produced by administration of parathyroid hormone or irradiated ergosterol caused functional disturbances in the activity of the higher nervous centers. These disturbances were characterized by an exaggeration of the inhibitory process, shown by enhancement of the inhibitory after-effect of negative stimuli, acceleration of the extinction of established conditioned reflexes, decrease and eventual disappearance of conditioned reflexes, and varying degrees of lethargy. This exaggeration of inhibition could be temporarily dispelled by the administration of caffeine. A temporary phase of excitation was noted at certain times during the administration of parathyroid hormone, but not during the administration of irradiated ergosterol. The various types of treatment, which involved the maintenance of a marked hypercalcaemia over considerable periods of time, had little effect upon the health of the animals in general, or the sense of hearing in particular.—R. G. H.

**Studies of calcium and phosphorus metabolism; in hypoparathyroidism and chronic steatorrhea with tetany with special consideration of the therapeutic effect of thyroid.** Aub, J. C., F. Albright, W. Bauer and E. Rossmeisl, J. Clin. Investigation, **11:** 211. 1932.

The metabolic findings in a case of post-operative parathyroid tetany are contrasted with those in a case of tetany with steatorrhea. The two conditions were found to have the following points of similarity: a low serum calcium level and a low urinary calcium excretion. Tetany with steatorrhea, however, differed from hypoparathyroidism in that the serum phosphorus was low instead of high, the fecal calcium excretion was high instead of low, and the urinary phosphorus excretion was high instead of low. Metabolic data were given which showed that thyroid medication in hypoparathyroidism raises the serum calcium, increases the calcium excretion in the urine, and increases the phosphorus excretion in the urine without affecting the blood phosphorus. The kidney thresholds for calcium and inorganic phosphorus were discussed.
—F. A. Albright.

**Irradiation of the parathyroids in generalized osteitis fibrosis cystica; report of a case.** Cutler, M. and S. E. Owen, Surg., Gynec. and Obst. **59:** 81. 1934.

A case is reported of a man, age 43, whose illness began 7 years previous to time of report. The first symptoms were general weakness and fatigue on exertion. Then there developed severe pains in the hip, back, neck, and head. He gradually lost control and use of his legs and was confined to bed. On admission he was unable to move his legs and complained of stinging sensation and numbness in both. He was poorly nourished and the muscle showed marked hypotonicity. There was a diffuse tenderness throughout the entire skeletal system. Muscular atrophy was marked. Upon x-ray examination the bones showed the characteristic picture of generalized osteitis fibrosis cystica. The blood calcium was 29.4 mg. per 100 cc. Radiation therapy over the four parathyroids was instituted. This was supplemented by high vitamin and high calcium diets. Two weeks after treatment the patient began to regain the normal use of his legs and the paraplegia completely disappeared. His strength increased. The pains diminished in some areas and disappeared in others. The appetite improved and there was marked improvement in the tonicity of the muscles. Ultimately, there appeared marked regeneration of bones. Many of the cystic areas disappeared and the bones assumed normal density.—R. G. H.

**On the question of the endocrine pathogenesis of the fibrous osteo-dystrophies (Sur la question de la pathogénie endocrinienne des ostéo-dystrophies fibreuses).** Khvoroff, B., Rev. franç. d'endocrinol. **11:** 260. 1933.

Following a review of the theories as to the etiology of the group of bone affections which the author prefers to classify as the fibrous osteo-dystrophies, i.e., the localized and generalized forms of osteitis fibrosa cystica, giant cell

tumor, and osteitis deformans, the author focuses his attention on the generalized form of osteitis fibrosa cystica and endeavors to convert a long since converted medical profession to the theory of its parathyroid origin on the basis of a single personal observation in which a parathyroid adenoma the size of a hen's egg was successfully removed.—C. C. Franseen.

**Effect of parathyroid extract on blood coagulability (Die Beeninflussung der Blutgerinnung durch Nebenschilddrüsenextrakt).** Marx, J., Arch. f. klin. Chir. **175:** 547. 1933. Abst., J. A. M. A. **101:** 817.

Marx reports three groups of experiments on the effect of injections of parathyroid extract on the bleeding time and the coagulation time of blood. Parathyroid extract was administered to rabbits and to normal men. Some time later, after the effect had worn off, the same animals and men were given calcium intravenously. It was found that the parathyroid extract, 25 minutes after its introduction, reduced the coagulation time by 12.4% and, from 18 to 24 hours later, by 14.8%. The calcium, 25 minutes after injection, reduced the coagulation time by 2.4%, and this effect was no longer in evidence when tested at later periods. While the parathyroid hormone was capable within 25 minutes of reducing the bleeding time by 11.6%, the calcium was without any effect. The parathyroid hormone reduced within 30 minutes the coagulation time in normal men by 26.4%, while the calcium was able to reduce it by only 8.2%. The effect of parathyroid hormone was still in evidence 24 hours later, as it was still capable of diminishing the coagulation time by 8.8%. Calcium had no such effect at this time. The bleeding time was not affected by either agent. However, repeated injections of parathyroid extract were able not only to reduce the coagulation time by 35.1% but likewise to reduce the bleeding time by 21%. A rise in the blood calcium level is not necessary for the reduction of the coagulation or for the bleeding time. The author was able, with the aid of parathyroid extract, to reduce in cholemic dogs the coagulation time of the blood by 33.7% and the bleeding time by 28%. On the basis of his animal experiments, the author recommends the injection of parathyroid extract in patients with jaundice one-half hour before the operation in preference to calcium injections.

**Tumors of the parathyroid gland; report of two cases.** Rankin, F. W. and J. T. Priestley, Am. J. Surg. **20:** 298. 1933.

Surgery of the parathyroid glands has been limited in the authors' experience to those cases which present the typical syndrome now recognized as hyperparathyroidism. The criteria for diagnosis have been, in brief: history of skeletal pain and weakness, roentgenographic evidence of generalized bony decalcification, negative calcium and phosphorus balance, and certain secondary findings, such as loss of weight, generalized myotonia, anemia and gastrointestinal disturbances. The presence of a palpable tumor in the region of the thyroid gland is not essential to the diagnosis. At the present time there seems to be insufficient evidence to warrant broadening the scope of surgery of the parathyroid glands to include such diversified maladies as osteomalacia, Paget's disease, rickets, chronic deforming arthritis and generalized myasthenia, although experimental clinical work in these fields may alter present opinions. Two cases in which parathyroid tumors were removed are reported, with follow-up records.—Authors' Abstract.

**Observations on effect of calcium on action of cocaine.** Salant, W. and W. M. Parkins, J. Pharmacol. & Exper. Therap. **49:** 67. 1933.

Intravenous injections of cocaine into cats, which were ineffective when the concentration of blood calcium was normal or above, stimulated intestinal contractility when it was reduced by oxalate or by thyroparathyroidectomy. Blood pressure remained unchanged or was decreased by cocaine in calcium depletion, but a rise of blood pressure followed its injection when calcium was normal or higher. Ergotamine intensified the effect of cocaine on the intestine in oxalated animals but it was without effect on the response of the circulation indicating that the reversed action of cocaine caused by calcium was cardiac in origin.—Authors' Abst.

**The action of sodium oxalate in normal and thyroparathyroidectomized cats.** Salant, W. and W. M. Parkins, J. Pharmacol. & Exper. Therap. **49**: 117. 1933.

No change in blood calcium occurred after the first and second dose of 20 mg. sodium oxalate per kilo given subcutaneously at 24-hour intervals. A progressive fall was produced by the next three injections of these amounts, given at such intervals, the maximum loss of calcium being 25%. Forty mg. oxalate per kilo, in divided doses given at intervals of a few minutes, produced a very moderate decrease of calcium in some and a reduction of 13-25% in a larger number of experiments. The loss after 80 mg. oxalate per kilo was 11-36%. The loss of blood calcium after intravenous injections produced by a dose of 30 and 40 mg. oxalate per kilo was 11-20% and 34-38%, respectively in a few minutes and slightly greater within 1 and 1¼ hours after injection. Some recovery of the blood calcium after intravenous injections of oxalate was noticed within four hours and was completed in about 24 hours. After subcutaneous injection blood calcium was normal in 24-30 hours when small and medium doses were injected and in 45-51 hours after larger doses. The decrease of blood calcium in thyroidectomized cats by oxalate given intravenously was more constant and was absolutely as well as relatively smaller, while the recovery was also slower than when the same amounts were administered to normal animals. Decrease of parathyroid hormone in the circulation, due to the toxic effect of oxalate in the parathyroids or absence of hormone on account of removal of the glands, was given in explanation of the effects of oxalate on blood calcium.—Authors' Abst.

**The effect of parathyroid extract on insulin secretion (Action de l'extrait parathyroïdien sur l'insulino-sécrétion).** Zunz, E. and J. La Barre, Compt. rend. Soc. de biol. **112**: 1544. 1933.

In dogs parathyroid hormone, when injected into a donor animal, reduced the blood sugar of an adrenalectomized receptor united to the donor by pancreatico-jugular anastomosis. Decapsulation of the donor made no difference. Parathyroid hormone did not increase the output of adrenin. The reaction failed if the pancreas was removed. Parathyroid extract produces hypoglycemia, therefore, by direct action on the pancreas.—J. C. D.

**Influence of the pineal gland extract on calcium metabolism (Action de l'extrait pineal sur la calcemie).** de Candia, S., Rev. franç. d'endocrinol. **9**: 23. 1931.

It is suggested that the pineal gland influences the nervous center of the calcium metabolism, which may lay in the region of the diencephalon. Four series of experiments were made. On normal persons the Ca level in the blood was determined before, and for 5 consecutive days after, administration of pineal extract equivalent to 0.2 to 0.4 grams of fresh gland by mouth or injection. A decrease of the serum Ca level was observed in three cases; it remained constant in one case; and was augmented in four cases. Seven dogs form the second group, and were studied before, one-half, and one hour after injection of 2 cc. of extract (0.2 grams fresh gland). In five a notable augmentation of the Ca level of the serum was observed. Maximum response occurred one-half hour after the injection. The influence of pineal, testicular and ovarian extract on the Ca level of the blood was studied on six normal subjects. An augmentation of the Ca level was observed in all subjects receiving pineal extract, while the Ca level decreased in those receiving testicular or ovarian extract. Metabolic studies in 3 normal humans after a diet constant in Ca conclude the series. Serum Ca levels were observed before, one-half, one, six and 24 hours after 2 cc. of the pineal extract and 10 cc. of 10% calcium chloride were injected into a vein. Twenty-four-hour urines from the day previous to, and from the day of the injection were collected, and the Ca excretion determined. The Ca in serum increases after pineal extract plus calcium chloride, but unlike parathyroid hormone, a retention of Ca took place, as demonstrated by a positive Ca balance between intake and urinary output.
—R. J. Wagner.

**The passage of the follicular hormone through the rabbits' placenta (Le passage de l'hormone folliculaire à travers le placenta du lapin).** Skowron, S. and B. Skarzynski, Compt. rend. Soc. de biol. **112**: 1604. 1933.

Rabbits were given folliculin in the later stages of pregnancy. The fetuses from these animals with the fluid surrounding them showed a higher folliculin content than did those from normal animals.—J. C. D.

**Internal secretion of the spleen (Zur Frage der inneren Sekretion der Milz).** Lauda, E., Wien. klin. Wchnschr. **45:** 989. 1932.

In four rats in parabiosis it was found that after splenectomy of one of a pair there was no change in the carbohydrate tolerance. After splenectomy of the second of the pair there was an elevation of blood sugar.—M. O. L.

**Effect of thymus extracts on survival after adrenalectomy (Influenza di un estratto timico sulla sopravivvenza degli animali bilateralmente surrenalectomizzati).** La Grutta, L. and L. Avellone, Riv. di pat. sper. **11:** 201. 1933. Physiol. Absts. **19:** 333.

Extracts made from the thymus with the technique used by Hartman for the separation of the active principle of the adrenal cortex were found capable of prolonging the life of adrenalectomized cats. Twelve animals were operated upon: 5 left without any treatment died within 18-36 hours; 5 receiving injections of thymus extract survived 36-94 hours; and 2 receiving extract of adrenal cortex survived 96 and 168 hours.

**Effect of folliculin on thyroid (Accion de la foliculina sobre la tiroides).** Bialet-Laprida, Z., Rev. Soc. argent. de biol. **9:** 245. 1933.

The thyroid gland of castrated rats 69 days after operation showed no significant change from normal on histological examination. Diminished activity as shown by large vesicles, low epithelium, pale colloid, was seen in thyroids from 14 castrated rats injected with 2 rat units of folliculin during 30 days before and 30 days after an ovarian graft. The same aspect was seen in thyroids from 7 rats which had received 2 rat units of folliculin only during 30 days after the graft was made, this operation being performed 30 days after castration. Castrated rats grafted with ovarian tissue but not treated with folliculin had normal thyroids. Another series (11 rats) received 2 and 5 rat units of folliculin daily some time before puberty (1st oestrus) till they had attained 150 grams weight. In 7 animals the microscopical aspects of the gland was that of hypofunction. The thyroid weight of rats injected with folliculin was below normal. In a 172-gram rat castrated, grafted and folliculin-treated the thyroid weight was 21 mg. and it was 18 mg. per 150 grams body weight for the folliculin-treated animals. Normal thyroid weight for animals of this weight as given by Donaldson and Houssay is 25 to 30 mg. It is concluded that folliculin inhibits the thyroid either by direct action or indirectly through the anterior pituitary.—J. T. L.

**Exophthalmic goiter in children of ten and under; comments based on a series of 102 cases.** Bram, I., Pennsylvania M. J. **37:** 45. 1933.

A series of 102 cases of exophthalmic goiter in children ten years old and under is reported. These constituted approximately 0.8% of a total of nearly 13,000 cases of goiter observed during a period of 22 years. Of this series only 5 occurred in males, the ratio of females to males being approximately 20 to 1. While in Bram's experience the exciting cause of exophthalmic goiter in adults is usually a psychic trauma, in children it is commonly a focal or general infection. The symptomatology in children, especially the thyroid swelling, exophthalmos, tachycardia, and nervous phenomena, is somewhat exaggerated as compared to that of adults. Since young children are apt to need their entire thyroid for future growth and development, treatment should lean toward conservatism. Elimination, at the proper time, of discoverable infectious foci; an ample low animal protein dietary; a proper rest routine, and a few carefully selected medicaments with psychotherapy dominating the patient and household, should effect recovery in the average child within several months of patient teamwork.—Author's Abst.

**An electrical method for use in the diagnosis of diseases of the thyroid gland.** Brazier, M. A. B., Lancet, **2:** 742. 1933. Abst., Physiol. Absts. **18:** 588.

The author's method for the investigation of the impedance of the human body to an alternating current has here been applied to the study of the thyroid disease. It is shown that in hyperthyroidism the impedance angle of the patient varies from the normal in such a way as to form a very reliable diagnostic test for toxic conditions of the thyroid. In this respect it is more spe-

cific and more certain than the basal metabolic rate. The test itself is open to less experimenal error than the basal metabolic rate estimation, and is particularly adaptable to the investigation of out-patients.

**Leg ulcers due to thyroid dysfunction.** Cohen, M., J. A. M. A. **102:** 283. 1934.

A case of deep ulcerations of the lower extremities associated with myxedema is described. The administration of thyroid extract was followed by rapid healing of ulcers that had persisted unchanged for 6 years. A relationship between circumscribed myxedema of the legs and leg ulcers of obscure etiology is suggested.—M. O. L.

**The use of 2:4-dinitrophenol as a metabolic stimulant.** Dunlop, D. M., Brit. M. J. No. 3820, 524. 1934.

The author administered dinitrophenol to 8 patients in varying doses. The oxygen consumption was increased by as much as 50% in doses of no more than 3 mg. per kilo of body weight. In such dosage it was found rather ineffective in lowering body weight. Even in maximum therapeutic doses it proved to be less effective than thyroid substances. For weight reduction it cannot be substituted for thyroid material in the treatment of myxoedematous states.—R. G. H.

**The oxygen consumption of animal tissue after thyroxine administration Sauerstoffzehrung tierischer Gewebe nach Thyroxineingaben).** v. Euler, H. and R. Enderlein, Biochem. Ztschr. **261:** 226. 1933. Abst., Physiol. Abst. **19:** 261.

The effects of administration of carotene and thyroxine to rats on the oxygen consumptions of the liver, kidney, and muscle tissues were investigated. Carotene administration caused an increase in the oxygen consumption of liver tissue. Injection of thyroxine caused a rise in oxygen consumption for all 3 tissues, but the increase was more marked in liver tissue than in kidney or muscle. Repeated thyroxine injections produced a rise of about 25% in the oxygen consumption of the liver.

**The morphology and physiology of the salamander thyroid gland; further experiments on the thyreo-activator.** Figge, F. H. and E. Uhlenhuth, Physiol. Zoöl. **6:** 450. 1933.

Previous work has shown that injection of extracts of the bovine anterior lobe produce metamorphosis in normal salamander larvae, but not in thyroidectomized larvae. It is therefore concluded that the anterior lobe contains a specific thyroid activating hormone, the "thyreo-activators." Crew, Weisner, Paal, Spaul, and others have disagreed with this concept. Spaul reports that the injection of anterior lobe extract produces metamorphosis in thyroidectomized Mexican axolotls. The injection of the thyreo-activator was therefore repeated using Colorado axolotls. Five series of animals were injected. Normal controls were injected with muscle extract. Normal animals were injected with thyreo-activator (A. L.). Thyroidectomized, hypophysectomized, and thyreo-hypophysectomized animals were injected with (A. L.) thyreo-activator. The injection of muscle extract had no appreciable effect on the metamorphosis or thyroid morphology of the controls. Normal animals injected with thyreo-activator metamorphosed after 6 to 8 injections and the thyroids were found to be activated. Thyroidectomized larvae remained unchanged after 33 injections. Hypophysectomized larvae metamorphosed after 9 injections and the thyroids were found to be activated. The thyreo-hypophysectomized larvae were unchanged after 35 injections. The injection of thyreo-activator produced metamorphosis in Colorado axolotls only if the thyroids were present. Therefore, it is again concluded that the anterior lobe secretes a specific "thyreo-activator."—Authors' Abst.

**Hormone regulation of purine metabolism (Die hormonale Regulation des Purinstoffwechsels).** Flossner, O., F. Kutscher and W. Wittneben, Ztschr. f. Physiol. Chem. **220:** 13. 1933. Abst., Physiol. Absts. **19:** 332.

In human subjects deprived of thyroid or suffering from thyroid deficiency, disturbance of purine metabolism is observed. The purine base fraction in the urine is increased manyfold. Adenine is the base chiefly concerned

in this rise, and about 64 times the normal amount of adenine may be excreted. When the patient has been given enough thyroxine to produce a definite clinical improvement, it is found that the adenine and other purine base excretion has fallen almost to normal. Lysinuria also occurs during thyroid deficiency. In the normal organism lysine not needed for protein synthesis is completely oxidized, but in the thyroid-deficient organism lysine is excreted. This lysinuria vanishes upon treatment with thyroid.

**Histological study of the thyroid gland in the guinea pig after irradiation (Etude histologique de la glande thyroide du cobaye après irradiation).** Florentin, P. and J. Watrin, Compt. rend. Soc. de biol. **112:** 670. 1933.

Weak doses of x-ray produce signs of extreme activity in the thyroid gland. These include cellular proliferation, increased secretory activity of the cells, and resorption of colloid.—J. C. D.

**Treatment of chronic heart disease by lowering the metabolic rate; the necessity for total ablation of the thyroid.** Friedman, H. F. and H. L. Blumgart, J. A. M. A. **102:** 17. 1934.

Roentgen irradiation of the normal thyroid gland, used alone and also as an adjunct to maximal subtotal thyroidectomy, failed to produce any appreciable persistent lowering of the basal metabolic rate in six patients with chronic heart disease. In one case, previously reported, in which a maximal subtotal thyroidectomy had been performed, both roentgen irradiation and a subsequent surgical attempt to remove the remaining fragments of the thyroid tissue were unsuccessful, and the clinical condition was not improved. One patient whose condition remained the same in spite of massive irradiation showed conspicuous improvement coincident with the reduction in the basal metabolic rate when the entire thyroid gland was removed according to the technic previously described by Berlin. The failure of others and of the authors to benefit patients by subtotal thyroidectomy, unsuccessful attempts to remove residual fragments at a subsequent operation, and the ineffectiveness of roentgen irradiation on the remaining tissue emphasize the therapeutic importance of removing the entire gland at the time of the first operation. Confirmation for this conclusion was obtained by experience in some 50 cases of angina pectoris or congestive failure, in all of which the clinical improvement has been conspicuous.—M. O. L.

**Effect of intravenous fluoride injections on erythrosedimentation in hyperthyroidism (La fluoterapia por vía endovenosa produce el descenso y normalización de la eritrosedimentación acelerada de los hipertiroideos).** Goldemberg, L., Rev. Soc. argent. de biol. **9:** 550. 1933.

In 5 cases a gradual slowing and a return to normal sedimentation time was seen, together with a lowering of the basal metabolic rate and pulse rate, and an increase in body weight.—J. T. L.

**Blood studies in hyperthyroidism.** Gottlieb, R., J. Lab. & Clin. Med. **19:** 371. 1934.

Morphological blood studies were made in 14 patients with hyperthyroidism before and after therapy. In 7 cases the morphology of the blood taken from the thyroid artery was compared with the blood of the thyroid vein. The phagocytic ability of the leucocytes of 6 patients with hyperthyroidism was studied. Hyperthyroidism was produced experimentally in 3 cats by means of thyroxin. Morphological blood studies were made and compared with 3 normal control cats. Kocher's blood picture was found to be present in practically all cases of hyperthyroidism. In addition as a striking observation an increase in the segmentation of the neutrophiles was noted, a shift to the right. Although the shift to the right may not be specific for a thyroid disturbance, just as Kocher's blood picture is not specific, it must still be considered as a considerable aid in the diagnosis, since it is not frequently observed in other pathologic conditions. The erythrocytes and thrombocytes are not strikingly diminished, but low normal or slightly subnormal figures are usually present. In other words, the whole blood picture is that of a definitely depressed myeloid system. The same is apparently true in experimental hyperthyroidism. The diminshed phagocytosis of the neutrophiles, being apparently due to an abnormal serum, together with the whole picture of myeloid depres-

sion all speak rather for a toxic influence of the thyroid gland. The lymphocytosis, although mostly relative, is also absolute. Whether we are dealing with a general compensatory proliferation of the lymphatic tissue, or whether the proliferation is specific in the pathogenesis of the condition, cannot be decided so far. The presence of the proliferation, however, is definite and quite apparent in the comparison of the thyroid artery and the thyroid vein. I would like here to refer to the work of Hellman, Heiber, Schlemmer, and others who believe the germinal centers of the lymphatic tissue to be a protective mechanism in the distribution of poisons and toxins. Aschoff in his excellent dissertation on the lymphatic organs does not quite accept this view, since there is not enough proof for the statements; he accepts, however, the possibility of such a protective mechanism.—Author's Abst.

**The effect of thyroidectomy and thyroid feeding on the milk secretion and milk fat production of cows.** Graham, W. R., Jr., J. Nutrition, **7**: 407. 1934.

Thyroidectomy itself causes a marked lowering of the milk fat secretion distinct from that produced after a control operation in which the thyroids were not involved. The diminution in milk secretion following removal of the thyroid gland cannot be readily distinguished from that accompanying control operations. However, the removal of desiccated thyroid glands from the diet of thyroidectomized cows causes a distinct decline in mammary secretion. The addition of small amounts of thyroid to the diet of either thyroidectomized or unoperated normal animals when the curve of lactation is falling, causes a rapid rise in the milk and milk fat production to a higher level from which the gradual fall, normal at this period in the lactation cycle, continues. Feeding excessive quantities of thyroid to a thyroidectomized animal caused a diminution in the milk secretion and fat production. From the reduced percentage of fat in the milk at this time, it appears that the reduction in fat production is greater than that in milk secretion. The effects observed are apparently related to the action of thyroid on general metabolism.—Author's Abst.

**Experimental and clinical studies of the relationship of thyroid disease and pancreatic function.** Hinton, J. W., P. C. Morton and C. Weeks, Ann. Surg. **99**: 126. 1934. Abst., Surg., Gynec. & Obst. **58**: 557.

The authors report a study of the production of colloid goiter in dogs by ligation of the pancreatic ducts. This ligation is thought to influence protein digestion and hence the supply of tyrosine, it being assumed that thyroxin is formed from absorbed tyrosine. These theoretical considerations are discussed and the technique of the ligation of the pancreatic ducts is described. Histological sections of dog thyroids before and three months after the ligation are shown. Some increase in colloid was evident. Thyroxin decreases colloid, and iodine increases it further. Determinations of tyrosine and tyramine in the blood of patients with low normal and high metabolic rates showed a parallel increase of values with an increase in the metabolic rate.

**Status lymphaticus; an adrenal-thyroid syndrome.** Kemp, W. N., Canad. M. A. J. **29**: 506. 1933.

Status lymphaticus is an undisputable clinical entity in Vancouver, B. C. There have been recorded 47 sudden and unexpected deaths in infants and young children in eight years. Death in these cases almost invariably occurred during sleep. Post-mortem examination always revealed a moderately enlarged thymus gland and enlarged mesenteric lymphatic glands. The signs of a non-fatal attack of the status lymphaticus syndrome are discussed. They are air-hunger, often accompanied by croupy respiration and cyanosis or pallor and collapse. The attacks are often preceded by fits of crying and temper. Sometimes there appears to be an immediate cause of the "attack" in the form of fatigue, fright, exposure to cold or a temper tantrum. It is the purpose of the article to show that there exists a remarkable correlation between the thymus, thyroid and adrenal glands; that status lymphaticus is in essence a dysfunction of the adrenal cortex which is more likely to occur in infants under one year (when the adrenal cortex undergoes involution and regeneration) in whom there probably exists in addition, a partial thyroid dysfunction due to a total lack of iodine in the cows' milk usually fed to these children in Vancouver. The enlargement of the thymus gland is considered as secondary to thyroid-adrenal dysfunction. This theory is developed by comparison of

the clinical signs and autopsy findings in cases of status lymphaticus with clinical signs and autopsy findings in cases of Addison's disease and Graves' disease in young adults together with the signs and autopsy findings of experimental bilateral, partial as well as complete, adrenalectomies. All factual knowledge thus gained points to the likelihood of status lymphaticus being the result of cortico-adrenal and thyroid dysfunction in humans. The author suggests the treatment of mild cases of status lymphaticus by opotherapy to prove or disprove the theory offered.—Author's Abst.

**The effect of calcium on the storage of colloid in the thyroid gland.** Klein, J., Ann. Int. Med. **7**: 1080. 1934.

Thirty-six young white rats, 250 to 300 grams in average weight, were separated into 6 groups, which were kept separate in clean wire cages and were all fed a liberal general diet. Group 1 received distilled water for drinking and daily injections of 0.5 cc. of a 2% hog thyroglobulin. Group 2 was given 5% calcium lactate water for drinking, and daily injections of 0.5 cc. of a 2% solution of thyroglobulin. Group 3 received distilled water for drinking, daily injections of thyroglobulin, and a daily subcutaneous injection of 1 cc. of a 10% solution of calcium gluconate. Series 1 to 3 were started on April 27, 1932, and were terminated by chloroforming on May 16, 1933. The thyroids were immediately dissected out, measured, and fixed in 10% formalin. Group 4 was given 1% potassium iodide in distilled water for drinking and no calcium. Group 5 received 1% potassium iodide in distilled water for drinking, and daily injections of 1 cc. of a 10% solution of calcium gluconate. Groups 4 and 5 were begun on May 20, 1933, and chloroformed on June 20, 1933. In group 4, two rats died of intercurrent infection. These were rejected. A series of 6 rats on the general laboratory diet and tap water served as controls. The thyroid tissues were imbedded in celloidin and sections 10 to 15 microns thick were stained with hematoxylin and eosin. Thick sections were chosen because they give a better concept of the shape and size of the follicles. Measurements of the follicles were made with an ocular micrometer. In each animal the diameters of 25 of the largest follicles were measured in scattered sections of the series and the average follicular diameter computed. As a check, 100 additional follicles were counted in scattered sections of each rat series and the results tabulated. The findings indicate that calcium either by mouth or hypodermically (in the presence of excess of thyroglobulin and iodine) increases the amount of colloid in the thyroid gland. Intercurrent respiratory infection may cause a decrease of colloid storage and induced hyperplasia. But even so, calcium increased the storage of colloid. The therapeutic action of calcium in hyperthyroidism may be due to this property of increasing colloid storage in the presence of an excess of thyroglobulin.

—R. G. H.

**The hemopoietic disturbances induced in the albino rat by administration of thyroxin.** Latta, J. S. and Miriam Cromwell Benner, Am. J. Anat. **54**: 1. 1934.

In a study of the peripheral blood of albino rats following repeated injections of thyroxin marked irregularities in the total and differential cell counts were encountered. In all experimental animals there was an early steady rise in the percentage of reticulated erythrocytes later followed by a decrease in those individuals in which bone marrow hyperplasia was found as a response to the thyroxin treatment. The other consistent feature in the blood picture was an average increase of about 10% in the percentage of polymorphonuclear neutrophilic leucocytes with corresponding increase in the lymphocytic percentage. Under the influence of thyroxin marked bone marrow hyperplasia occurred, which was predominantly erythroblastic in character, involving granulopoiesis, however, to a lesser degree in most cases. Following injection of larger amounts, evidences of marrow aplasia were found. In the spleen and lymphatic nodes an increase in monocytes and macrophages was observed, particularly in the lymphatic nodes. In the latter organs, particularly the spleen, an increase in hemoglobin pigments was found following injection of thyroxin. The fundamental cause of these induced hemopoietic disturbances is believed to have been an increased metabolic rate, which in turn increased the rate of differentiation, delivery and subsequent destruction of the cells of the blood.—Authors' Abst.

**A study of the relation of dietary fats to action of thyroid extract in rats.** Loumos, S., Proc. Soc. Exper. Biol. & Med. **31:** 895. 1934.

The administration of cod liver oil to rats had a protective effect against the action of thyroid extract in causing loss of body weight. Olive oil first inhibited and then facilitated the action of thyroid extract and cocoanut oil augmented the action from the start.—M. O. L.

**Amenorrhea and oligomenorrhea associated with low basal metabolic rates.** Mussey, R. D. and S. F. Haines, Am. J. of Obst. & Gynec. **27:** 404. 1934.

A study of the effect of elevation of the basal metabolic rate was made in 27 patients with amenorrhea or marked oligomenorrhea occurring in association with low basal metabolic rates. No patients with evidences of myxedema were included in the study. The basal metabolic rates varied from —11% to —27%. Desiccated thyroid gland was given daily in doses sufficient to maintain the basal metabolic rates constantly between —5% and —8%; no other therapy was used. The condition of 13 (59.09%) of the 22 patients with amenorrhoea was improved after treatment. No patient in the group who had had amenorrhoea for more than one year was improved. Of the 5 patients with oligomenorrhea, 2 were better after treatment. Twenty-five of the 27 patients complained of fatigue or functional disturbances, which, in many instances, had preceded the menstrual disturbances by years, and 21 of these patients expressed themselves as in better general health after elevation of the basal metabolic rate. Elevation of the basal metabolic rate should be undertaken only when the patient can be kept under observation long enough to enable the establishment of a dose of desiccated thyroid which will raise the basal metabolic rate sufficiently and at the same time will not subject the patient to the risk of maintaining too great an increase in the rate.
—Authors' Abst.

**A pseudonephritic form of thyroid deficiency with kidney changes of the same origin (Forme pseudo-néphrétique de l'insuffisance thyroïdienne et altérations rénales de même origine).** Mussio-Fournier, J. C., Ann. de méd. **32:** 440. 1932.

The author reports four cases and discusses in detail 13 more from the literature of hypothyroidism with edema which simulates the clinical picture of nephritis. His conclusions are as follows: Due to a disturbance of the water and salt metabolism, hypothyroidism may produce at times a clinical picture similar to that of certain forms of nephritis. The symptomatology of this pseudo-nephritic form of thyroid insufficiency consists of: oliguria, soft edema, fluid in the serous cavity, retention of nitrogen, signs of so-called minor brightism and arterial hypertension. This syndrome may be observed even in cases which do not present any sign of cardiac insufficiency or cachexia of myxedematous origin. The persistence of the symptoms, in spite of the antinephritic treatment, and the disappearance or the alleviation of the same obtained with the administration of thyroid indicate their myxedematous origin as well as the integrity of the renal function. An important disturbance in the water and salt metabolism is undoubtedly one of the fundamental causes of the described syndrome. In some cases insufficiency of the myxedematous heart may contribute to the symptoms, but this pathological finding does not necessarily have to be present. Myxedema may produce renal pathology which is expressed in: albuminuria, granular casts, red cells, and delay in the elimination of phenolsulphonephthalein. Under the influence of thyroid medication these symptoms may disappear completely in some instances or partially in other, thus indicating the existence of lesions totally or partially reparable and caused by thyroid insufficiency. It is too early to try to specify the type of kidney pathology myxedema produces. The rôle of thyroid deficiency in the pathogenesis of nephrosis has not as yet been demonstrated. Outside of the pseudonephritic aspects of hypothyroidism, which are essentially due to a disturbance in the water and salt metabolism, one should know that the same symptoms can be equally produced by cardiac insufficiency or renal pathology, which are in themselves due to thyroid insufficiency. A simultaneous action of these mechanisms in the causation of the above described symptoms has been observed. Hypothyroidism may exaggerate the intensity as well as the duration of edema of different origin as, for example, nephritic edema, or even "hunger edema." Thyroid in such cases will greatly contribute in the absorption of the edema.—A. Rudy.

**A case of postencephalitic Parkinson's disease treated by total thyroidectomy.** Myerson, A. and D. D. Berlin, New England J. Med. **210:** 1205. 1934.

It was known that drugs that are effective in the treatment of Parkinson's disease lower the oxygen consumption rate. This fact together with a theory that lessening the strain on a defective mechanism would be helpful led to the initiation of complete surgical thyroid deficiency. The patient was a woman of 32 who was bed-ridden. The tremor was excessive. She was receiving 8 doses of hyoscine (gr. 1/50) and large doses of sedatives daily. The thyroid was removed and myxedema with a basal rate of —35 developed. It proved to be possible then to control the symptoms fairly well with only 3 doses of hyoscine and light doses of luminal daily. Under this regime with small doses of thyroid the clinical condition is much improved. Treatment with thyroid alone was ineffective. The research is being extended.—R. G. H.

**The heart in myxedema.** Ohler, W. R. and J. Abramson, Arch. Int. Med. **53:** 165. 1934.

Thirty-five cases of myxedema were studied, 13 of which showed abnormal changes in the electrocardiogram. The characteristic changes in the electrocardiogram are a decrease in voltage of all the complexes and frequently an inversion of the T waves in all the leads. Increased auricular-ventricular conduction time is seen in some cases. These abnormal electrocardiograms are seen with few exceptions when the basal metabolic rate drops to a level of —25 or lower. Enlargement of the heart revealed by roentgenograms is seen frequently in cases showing abnormal electrocardiograms. Sluggishness of cardiac contractions is demonstrated by fluoroscopy. The specificity of thyroid gland extract in these cases is shown, the electrocardiogram and the size of the heart returning to normal following treatment. Low, normal and high blood pressures are seen in myxedema. In patients with dilated hearts the pressure tends to be normal or subnormal. In the series reported, thyroid treatment tended to increase the blood pressures that were low and to decrease those that were high. Distant heart sounds and mild congestive failure are frequent clinical findings. The changes noted in this series are characteristic of the disease and warrant the use of the term, "myxedema heart." Attention is directed to the paucity of careful pathologic studies of the heart muscle in myxedema. A definite explanation of the cause of the cardiac changes in myxedema may not be possible until such a study is completed.

—Authors' Summary.

**Cellular function and the Golgi apparatus; renal and thyroid secretory activity (Fonctionnement cellulaire et appareil de Golgi. Sécrétion rénale et thyroïdienne).** Okkels, H., Compt. rend. Soc. de biol. **112:** 1691. 1933.

In observations based on over 100 guinea pigs half an hour after injection of anterior hypophyseal extract, the thyroid cells were swollen and had a limiting membrane at the apex. The Golgi apparatus had vanished. Half an hour later the Golgi apparatus had begun to reappear and the vesicular colloid was already vacuolated. Within 2 hours of injection the characteristic picture of hyperactitvity had been established with hypertrophy of the Golgi apparatus. The degree of enlargement of the apparatus closely paralleled the degree of sustained overactivity. The definite relation between Golgi apparatus and activity in the thyroid was in contrast to the lack of relationship found in the kidney.—J. C. D.

**The rational treatment of hyperthyroidism.** Pemberton, J. deJ., South. M. J. **27:** 323. 1934.

Three hundred cases of exophthalmic goiter and 300 of thyroid adenoma with hyperthyroidism in which operations were performed 2 to 7 years previously, were used as a basis for analysis. Of the former 69%, and of the latter, 68%, of the patients reported themselves improved. Iodine is of marked value as a preoperative measure. With its use the surgical mortality in exophthalmic cases was 0.83%, while that for adenomatous goiter with hyperthyroidism was 1.4%. Neither iodine, x-ray, nor other forms of non-surgical treatment were satisfactory in effecting permanent improvement.—J. C. D.

**The excretion of iodine in a myxedematous man after continuous administration of thyroxine (Über die Jodausscheidung beim myxödematösen Menschen nach fortgesetzter Thyroxinzufuhr).** Schittenhelm, A. and B. Eisler, Ztschr. f. d. ges. exper. Med. **86:** 299. 1933.

Thyroxine was administered intravenously to a patient with myxedema whose basal metabolic rates varied from —28.1% to —33.0%. The excretion of iodine in the urine and stools was determined before, during, and after the injections of thyroxine. The blood iodine and basal metabolic rate were determined at intervals. When the basal metabolic rate was low, the predominant excretion of iodine after injection of thyroxine was in the urine. When the basal metabolic rate had risen as a result of the thyroxine administered, the excretion of iodine following further injections of thyroxine was predominant in the stools, exactly as occurs in normal individuals. After stopping the administration of thyroxine, the iodine of the thyroxine which had been retained was slowly excreted, the predominance of excretion taking place in the stools. After intravenous injection of 26 mg. of thyroxine the basal metabolic rate rose 42%, or an average of 1.6% for each milligram of thyroxine injected. During this time it was estimated from studies of the quantity of iodine excreted that approximately 5 mg. of thyroxine was retained in the body, and therefore 1 mg. of retained thyroxine produced a rise of 8.4% in the basal metabolic rate. During this course of injection of thyroxine the amount of iodine in the blood rose rapidly; then fell to the normal level. After stopping the injections of thyroxine, the blood iodine fell back to its former low level in a few days.—S. F. Haines.

**The morphology and physiology of the salamander thyroid gland; the effect of the thyroid activator on thyroidectomized animals.** Schwartzbach, S. S. and E. Uhlenhuth, Physiol. Zoöl. **6:** 236. 1933.

Larvae of Amblystoma tigrinum were thyroidectomized; intraperitoneal injections of anterior-lobe extract were begun one day after the operation. In the normal control larvae these extracts produced metamorphosis after four to twelve injections. Of four thyroidectomized larvae, none metamorphosed after nine injections. One did not metamorphose after 44 injections, another one metamorphosed spontaneously. Careful examination showed regenerated thyroid remnants in the thyroidectomized animals which metamorphosed either after anterior-lobe injections or spontaneously. The inference is drawn that the thyroid activator extracted from the anterior lobe of the hypophysis is ineffective in producing metamorphosis if the animal's own thyroids are removed before injections are started.—Authors' Abst.

**The effect of thyroid hormone upon gill reduction in Triturus viridescens.** van Slyke, E., Physiol. Zoöl. **5:** 555. 1932.

In a large part of the population of Triturus from the Woods Hole region, the basal part of the larval gills are retained until adult size is reached. Such types have undergone many of the metamorphic processes; the final loss of all larval structures, however, progresses very slowly. These inhibited types are differentiated from the relatively rare cases of true neotenous Triturus, in which the animal is completely larval and sex mature (approximately 1% of these populations). The reported failure of such inhibited types to respond to thyroid with acceleration in completion of metamorphosis (Morgan and Sondheim, 1931) was not confirmed. It was found that injections of thyroid accelerated completion of transformation by 49% at 12° C. to 17° C. Low temperature inhibits such acceleration, and at 6° C. to 10° C. the acceleration was only 2%; low temperature (6° C. to 10° C.) in uninjected controls produced an inhibition of 10% in comparison with uninjected animals at 12° C. to 17° C. The evidence indicates that these forms are not to be classed with the Proteidae as types which do not respond to thyroid hormone.—Author's Abst.

**Will cretinism become endemic in Wisconsin?** Stoddard, C. H., Wisconsin M. J. **32:** 389. 1933.

Since 1895 a large incidence of goiter in the region of the Great Lakes has been recognized and given rise to a curiosity as to the apparent lack of cretinism found in the goiter belts of this country. The dictum of Morel that "Goiter is the first step on the road to cretinism" has seemed not to be borne out by the number of reported cases found here. The probable explanation is

that the region has been too recently settled, and too few generations have lived here to have transmitted this degenerative tendency. While Wisconsin was first settled in the decade of 1840-1850, the larger immigration has come only within two generations, a period scarcely sufficient to produce any large number of cretins at the present time. A list of 68 cases is given—mostly of the sporadic variety and largely of foreign ancestry, leaving the question as to endemic cretinism unanswered for the present. Many factors such as goiter prophylaxis and the use of sea foods and vegetables imported from non-goiter regions, may delay or even prevent an incidence of cretinism even in later generations to a degree comparable to that found in Switzerland. Nevertheless the finding of 68 cases in the face of the fact that recent writers state that no substantiated cases exist in the Great Lakes basin is of considerable interest and suggests that a more careful study of the records of institutions for the feeble-minded and of the lists of diagnoses in children's hospitals and dispensaries in those states known to have much goiter would show many more such cases than is usually believed.—Author's Abst.

**Hyperthyroidism and nutrition; vitamin B and thyroxin.** Sure, B. and M. E. Smith, J. Nutrition, **7**: 548. 1934.

It has been found that the albino rat can tolerate large doses of thyroxin for relatively long periods of time when administered orally to the full-grown animal on diets abundant in vitamin B. Collapse, however, takes place readily when the ration is deficient in this dietary essential. Subcutaneous injection of thyroxin is decidedly more toxic than oral administration. It has been found that a highly concentrated vitamin B extract from rice polishings exerts a remarkable protective influence in experimentally produced hyperthyroidism in the rat, and it is suggested to the clinician that oral or preferably parenteral administrations of potent standardized vitamin B concentrates may be indicated in toxic goiter, particularly in non-operative cases.—Authors' Abst.

**Acropachy; secondary subperiosteal new bone formation.** Thomas, H. M., Arch. Int. Med. **51**: 571. 1933.

The case is presented of a young colored man in whom diffuse goiter with hyperthyroidism developed for which subtotal thyroidectomy was performed. Eight months later he noticed clubbing of the fingers and brawny swelling of the legs, and when examined two years later was found to have an extreme degree of acropachy. A careful examination made at the time of operation and repeated on 2 further occasions, 2 and again 4 years after operation, failed to reveal other disease or lesion of the heart or lungs. Nothing is known concerning the mechanism of the bony change in this syndrome but an altered blood flow is suggested as the most plausible etiologic factor.—R. G. H.

**Pigment of the nails during hyperthyroidism.** Thomas, H. M., Jr., Bull. Johns Hopkins Hosp. **52**: 315. 1933.

The appearance of transverse bands of pigment on each of the finger nails of a colored woman suffering from diffuse goiter with hyperthyroidism is reported. Judging from the rate of growth of the finger nails the author infers that the pigment was laid down at the time when the patient received two exposures of radium to the thyroid gland. No explanation of the phenomenon is forthcoming. The pigment granules were found to be scattered through the entire thickness of the nail substance with a tendency for the deeper layers to be more pigmented than the superficial. They undoubtedly owe their color to the presence of melanin. Transverse stripes of pigment have never been described before. When this patient came to necropsy some time later no explanation was offered for the deposition of pigment in the finger nails.
—Author's Abst.

**Thyrotoxicosis in its relation to pregnancy.** Wallace, J. F., Am. J. Obst. & Gynec. **26**: 77. 1933.

The literature dealing with thyrotoxicosis in pregnancy is reviewed briefly. The author then analyzes nine cases of thyrotoxicosis occurring in 11,571 pregnancies, emphasizing the rarity of this complication in pregnancy. Of the nine patients, three did not have sufficient symptoms or signs to permit a definite diagnosis. Two patients were suspected of thyrotoxicosis prepartum and postpartum reactions were attributed to this condition. The remaining four cases

were mild and an abortion was performed in three of these. In discussing the management and treatment of hyperthyroidism complicating pregnancy the author indicates that the consensus of opinion is against abortion in these cases. Rest, sedatives and iodine are recommended in exophthalmic goiter and subtotal thyroidectomy in progressive or severe cases.—J. Lerman.

**The mechanism of the early relief of pain in patients with angina pectoris and congestive failure after total ablation of the normal thyroid gland.** Weinstein, A. A., D. Davis, D. D. Berlin and H. L. Blumgart, Am. J. M. Sc. **187**: 753. 1934.

Observations on the immediate postoperative relief of chest pain after total thyroidectomy in 19 patients are described. Data were collected before, immediately after and during several weeks after operation in 3 groups: (1) Changes in non-anginal precordial pain; (2) changes in areas of skin hyperesthesia and muscle and periosteal hyperalgesia of the chest wall; (3) changes in the character and distribution of pain of angina pectoris. Within a few hours after operation, non-anginal precordial pain, hyperalgesia and hyperesthesia disappeared, remained absent for 2 to 4 weeks, but then usually reappeared if the basal metabolic rate had not declined significantly. Only after the basal metabolic rate had dropped appreciably did the above-mentioned signs and symptoms diminish or disappear permanently. Studies were made on the distribution of the pain of angina pectoris produced under standard conditions in 3 patients and after hemithyroidectomy. The remaining half of the thyroid gland was removed at a later date. Exercise within 2 weeks after hemithyroidectomy produced no pain in the arm and the side of the chest corresponding to the side of operation. The pain of angina pectoris was experienced only on the unoperated side and usually stopped sharply at the midline of the sternum. The similarity of these findings to those after cervical sympathectomy and alcohol injection is discussed. The basal metabolic rate did not change appreciably after the first hemithyroidectomy. After 2 to 8 weeks, pain on exercise was again experienced on the operated side. Only after removal of the other half of the thyroid gland and after an appreciable drop in the basal metabolic rate was the pain of angina pectoris permanently relieved. These observations point definitely to the following conclusions: (1) The immediate relief of pain after total thyroidectomy is due to the interruption of afferent nerve impulses from the heart at the time of operation; (2) relief by this mechanism is only temporary; (3) permanent relief is related to the lessened work of the heart attendant on the development of the hypothyroid state. These findings indicate that, after total ablation of the thyroid, complete bed rest should be enforced, despite the early subjective relief experienced by the patient, until the basal metabolic rate shows significant lowering.
—Authors' Summary.

**Specially produced milk in the solution of the goiter problem.** Weston, W., South. M. J. **27**: 249. 1934.

Milk from various sources was analyzed for iodine. Milk containing a high iodine content was fed to an unspecified number of children with apparent good results.—J. C. D.